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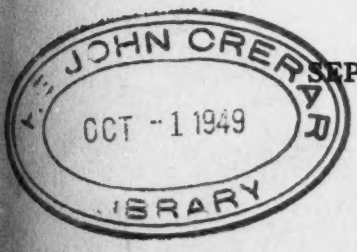

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Archives of Dermatology and Syphilology

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SUBOCCIPITAL DERMATITIS

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ST. PAUL

SUBOCCIPITAL dermatitis is presented frequently in every clinic or office and is a disorder of ill repute in that it is usually regarded as a stubborn and nonresponsive member of that notoriously difficult family, eczema. Discussion of dermatitis of the suboccipital fossa—when spoken of at all, the disease is called lichen simplex chronicus of the nape—is almost uniformly avoided by authors of standard textbooks. Duhring merely stated that the nape is a common site for eczema in the young or the old. Savill [1] offered a slightly more extensive discussion, though I disagree with her statements that "only rarely is there found a degree of moisture." She expressed the belief that the condition is largely due to the habit of scratching and said, "It provides a form of psychological relief from worry and mental tension." With reference to neurodermatitis, Barber [2] stated that "the most characteristic site, perhaps, is the nape of the neck, since here it is almost peculiar to women." He strongly advocated estrogenic therapy. Many papers on lichen simplex chronicus give brief reference to dermatitis of the nape or suboccipital fossa. My present concern is with two factors: (1) whether most instances of suboccipital dermatitis should be regarded as neurodermatitis and (2) whether neurodermatitis in this location has any important features different from those of neurodermatitis in general.

Clinicians have expressed various opinions as to the cause and nature of the chronic, inflammatory reaction frequently observed below the occipital prominence. Some have regarded it as psoriasis and others as seborrheic dermatitis, contact dermatitis or atopic dermatitis (neurodermatitis). For the first three of these diagnoses there seems inadequate evidence; also, one would have to make different diagnoses for various manifestations which are observed at that site. Differentiation of psoriasis is usually not difficult, since other more or less distant manifestations are of considerable assistance. Contact dermatitis seems to me rather easily recognized. Circumscribed sebor-

Read as the presidential address at the annual meeting of the Chicago Dermatological Society, Jan. 21, 1948. Introductory comments have been deleted.

1. Savill, A.: The Hair and Scalp, ed. 3, Baltimore, Williams & Wilkins Company, 1945, p. 146.

2. Barber, H. W.: Dermatoses of the Menopause, Practitioner **156**:333, 1946.

rheic dermatitis is a concept difficult to accept. To me it seems easier and more satisfactory to hold to a view of neurodermatitis (atopic dermatitis) sufficiently broad to accept almost all forms of dermatitis seen in this region. Immediately, one meets the difficulty of lack of general agreement as to terminology; classifications are arbitrary, and one may be satisfied to call this localized neurodermatitis. At the outset one may properly inquire whether this eruption deserves consideration separate from other localized manifestations of neurodermatitis, but I think the question should not be answered before the facts have been set out. Through this discussion I shall use the term neurodermatitis as synonymous with atopic dermatitis.

In preparing this presentation I have reviewed the records of a consecutive series of 83 patients with dermatitis localized to, or beginning in and extending from, the suboccipital fossa. The patients are divided into two groups: group A, those whose eruption was limited to the area under consideration (49 patients), and group B, those who had other manifestations of neurodermatitis (34 patients). Patients with vulvar or anal dermatitis were excluded from this study. The cases will be discussed with reference to clinical features, histologic manifestations, therapeutic response and etiologic considerations. During the same period I saw only 2 male patients with similar eruptions. Their eruptions were of long duration and responded poorly to treatment.

CLINICAL FEATURES

Dermatitis of the suboccipital fossa is sometimes referred to as lichen simplex chronicus; yet a review of the clinical features soon demonstrates the inaccuracy of general use of this appellation. The inflammatory reaction is more active than is that in ordinary lichenification, and there often are excoriations, traumatic dermatitis, superficial infection and dermatitis resulting from ill advised therapeutic applications. Next to itching, redness was found to be the commonest clinical feature and was usually associated with thickening and frequently with scaling, less often with crusting and excoriation. Clearcut lichenification was evident in only one fourth of the cases with eruptions limited to the single site, and was even less frequent when the patient presented other evidences of eczema. When not lichenified the eruptions remained relatively dry, and the tendency to moistness was seen usually as a result of excoriation, rather than in the form noted in nummular eczema, for instance. Lichenification was observed in 1 case in which the eruption had been present for six months, but it usually was present only when the disorder had lasted a year or more. Formation of a plaque was almost constant, with discrete papular elements observed infrequently. Unilateral involvement was relatively rare. There was considerable variation in the extent

of the eruption, but in most instances the plaque was practically limited to the fossa and its margins, being 1 to 2 inches (2.5 to 5 cm.) in diameter.

AGE

Investigation of ages of patients with suboccipital dermatitis showed that there is no significant difference between the age at onset in these two groups and in 738 female patients with neurodermatitis of other types. There was some decrease in incidence in the first and second decades of life and an increase in the 30 to 40 year age group, but these differences were not great.

TABLE 1.—*Ages of Women with Neurodermatitis*

Age, Years	Group A	Group B	All Patients with Any Type of Neurodermatitis
Total	49	84	738
Less than 20	14%	9%	15%
20 to 40	46%	45%	43%
More than 40	40%	43%	41%

TABLE 2.—*Association of Neurodermatitis with History of Atopy*

Age, Years	Group A	Group B	All Patients with Any Type of Neurodermatitis
Total	34	29	592
Less than 20	67%	67%	58%
20 to 40	70%	73%	63%
More than 40	50%	91%	50%
Average	62%	75%	58%

ATOPY

Patients were questioned for information relative to other recognized personal atopic disorders (hay fever, asthma or eczema in infancy or early childhood) and for the presence of these diseases in closely related members of their families. Of all female patients with neurodermatitis, there was a history of one or more of these features in 58 per cent, while 70 per cent of patients with suboccipital dermatitis gave such histories. Concerning the obvious inaccuracy of replies to such questions, I question whether this difference is significant.

For persons in group A over 40 years old the positive histories were fewer, even though added years had provided more time for atopic manifestations to become evident. The significance of these lowered figures need not be discussed, since they are characteristic for all women with neurodermatitis.

SEBORRHEA

Mild seborrhea, which was noted in approximately half the patients, is found in a proportion not greatly different from that for the entire population. Certainly, the incidence should be much higher and the inflammation severer if seborrhea were important in causing dermatitis at this site.

MENSTRUAL HISTORY

An abnormal menstrual history is frequently given by patients with "functional" disorders. Criteria of abnormality are difficult to establish but in this instance were arbitrarily selected; frequency of menstruation of less than twenty-four or more than thirty-two days, duration of less than four or more than six days or amounts spoken of as "scant" or "profuse."

Table 3 shows clearly that abnormal menstruation occurs much more frequently among women with suboccipital dermatitis than among

TABLE 3.—*Association with Abnormal Menses*

Age, Years	Groups A and B	All Patients with Any Type of Neurodermatitis
Total	49	455
Less than 20	27%	17%
20 to 40	45%	27%

all women with neurodermatitis. The presence of normal menstruation is of greater significance than is a history of abnormality in women over the age of 40 years. Above that age, normal menstruation is twice as common in all patients with neurodermatitis as in those with suboccipital dermatitis. It is concluded that there is a significant association between suboccipital dermatitis and ovarian dysfunction.

MICROSCOPIC PATHOLOGY

Histologic examination might have been expected to provide evidence for accurate differential diagnosis, but it did not, as I discovered on study of 29 specimens taken for biopsy and comparison of them with other specimens, of psoriasis of the scalp and seborrheic dermatitis. The difficulty lies not in the site involved but in the nature of the processes to be differentiated. Gans [3] pointed out differences in lichenified neurodermatitis, eczema and seborrhea, but the attempt seems forced, and the discussion is generally unsatisfactory. MacCardle and the Engmans [4] listed detailed features and concluded that they

3. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1, pp. 245, 263 and 275.

4. MacCardle, R. C.; Engman, M. F., Jr., and Engman, M. F., Sr.: Histology of Neurodermatitis, Arch. Dermat. & Syph. **44**:161 (Aug.) 1941.

could differentiate localized neurodermatitis from disseminated neurodermatitis or from chronic contact dermatitis. The extensive reports of Sachs [5] and his associates pointed out differences of degree rather than of kind (and left something to be desired in their unusual classification and use of the term "eczema"). Montgomery [6] clearly described the microscopic changes observed in various forms of eczema. He expressed the belief that the process in seborrheic dermatitis is not diagnostic and frankly stated that atopic dermatitis or neurodermatitis may not always be distinguished from psoriasis.

In dermatitis of the suboccipital fossa I observed the following changes. Hyperkeratosis was sometimes present but was neither

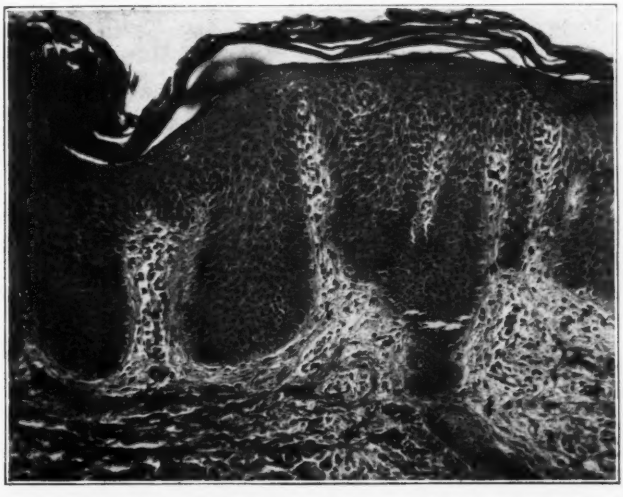

Fig. 1.—Section from lesion of suboccipital dermatitis, showing characteristic changes. There is a moderate amount of hyperkeratosis and parakeratosis, with acanthosis and clubbing of the rete pegs. Intracellular edema is accompanied with a few lymphocytes in the epithelial tissues above the papillae. Changes in the cutis are less extensive, though there are some edema and lymphocytic infiltration in the papillae.

constant in occurrence nor striking in degree. Parakeratosis was present fairly constantly but was not intense and was occasionally localized to small areas. The stratum granulosum was usually normal, though sometimes absent in areas showing parakeratosis. Acanthosis of moderate degree was rather constantly noted and was often asso-

5. Sachs, W.; Miller, C. S., and Gray, M. B.: Neurodermatitic Reaction, Arch. Dermat. & Syph. **54**:397 (Oct.) 1946.

6. Montgomery, H., in Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, pp. 247 and 1201.

ciated with elongation or clubbing of the rete pegs. Epithelial edema was commonly present, but only in slight to moderate degree, and in only 5 instances was there anything even slightly resembling vesiculation. Frequently one noted degeneration of individual cells or groups of several cells in the rete layer. When lymphocytes invaded these areas of degeneration, there was sometimes more edema and thus the development of a minute vesicle. Lymphocytes were occasionally noted singly or in groups of two or three, but no epithelial abscesses were observed. The cutis frequently presented some edema. The connective tissues often appeared swollen and fragmented. Special

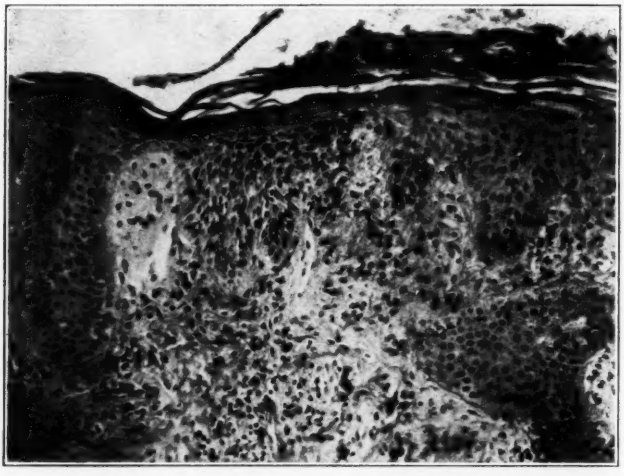

Fig. 2.—Section showing more acute inflammation with disarrangement of structure, more parakeratosis and more and deeper infiltrate than are shown in figure 1. Seldom were such changes noted in suboccipital dermatitis.

stains showed that the elastic tissue was often greatly decreased or fragmented; the collagen fibers were frequently degenerating and fragmented, even though the eruption had not been present long. Capillary dilatation was commonly present and was frequently associated with congestion. Thickening of the walls of larger vessels is difficult to evaluate but seemed to be present in 10 instances. Cellular infiltrate was always present and consisted almost exclusively of lymphocytes, oftener small than large. Frequently there were aggregations of young or wandering connective tissue cells. A few polymorphonuclear leukocytes were also present in many instances. Eosinophils were rare, and red blood cells were seen only occasionally. The

infiltrate tended to involve the upper portion of the cutis earlier and more constantly but in later stages might be either perivascular or diffuse in distribution. It was not perifollicular.

On reviewing the aforementioned changes, one might think that psoriasis could be differentiated rather easily, but study of sections from psoriatic lesions of the scalp showed that in this area one does not constantly observe the changes regarded as characteristic of psoriasis. Sections from seborrheic dermatitis showed changes different in degree rather than in essential features; there were perhaps more edema, acanthosis and cellular infiltration. In general, the microscopic process can be differentiated from that of contact dermatitis. Sections from suboccipital dermatitis show the changes which Sachs spoke of as "the neurodermatitic reaction" and correspond well with Montgomery's description. The changes in the connective tissues in this disorder seem to have been greater than those that were mentioned in Sachs's and Montgomery's descriptions.

THERAPY

Unfortunately, but not surprisingly, the therapeutic attempts were so varied that one can hardly say what regimen was most satisfactory. Topically, most patients were asked to try boric acid ointment or a mild (6 to 10 per cent) ammoniated mercury ointment. If these were noneffective, 1 per cent of phenol may have been added to the former, or 5 to 10 per cent of ichthammol N. F. or 1 to 3 per cent of crude coal tar was incorporated in an oxycholesterol-petrolatum ointment base (aquaphor®) or fatty acid esters of diethanolamine with petrolatum (hydrosorb®) or, less frequently, in a soft zinc oxide paste. Roentgen radiation was used in most cases (but not if it had been previously given by others), in fractional doses, such as 75 r, beginning with weekly intervals and gradually tapering off, seldom exceeding six to nine treatments. Diffuse seborrheic features were treated when present, but this procedure was not emphasized and in some cases was deliberately ignored in order to determine that such treatment is not necessary, though it may be helpful.

While some patients responded rapidly to simple measures, it seemed that many required attention to general hygienic improvement, such as regularity of hours, avoidance of overwork, adequacy of sleep and avoidance of persons or circumstances having frustrating or otherwise irritating influences; or, less successfully, an attempt was made to change the patient's reactions to such influences. As an adjuvant, sedation was frequently prescribed, not as nocturnal hypnosis but in the form of phenobarbital, ½ grain (0.03 Gm.), or N-methyl phenobarbital (mebaral®), 1½ grains (0.09 Gm.) given twice or three times

during the waking hours. Estrogens were not prescribed unless the patient was in the postmenopausal period or gave a history suggesting estrogenic deficiency; estrogens were sometimes given by injection but more often orally, in the form of diethylstilbestrol, 0.25 to 1.0 mg., or estrogenic substances, water soluble (premarin®), 1.25 mg., on retiring. Their chief effect is probably by way of general relaxation and related emotional mechanisms rather than by direct chemical and physiologic influences on the skin.

RESPONSE TO THERAPY

Therapeutic response was analyzed in those cases in which there was sufficient observation. Table 4 gives the results in each group, those without and those with other eczematous manifestations. In the first group the records of 36 cases were reviewed, and in 30

TABLE 4.—*Response to Treatment*

Duration of Disease Previous to Treatment	Good Results			Fair	Recurrences	No Response
	Within 2 Mo.	At 2 to 4 Mo.	After 4 Mo.			
Group A						
Less than 3 mo.	2	3	..	2	..	2
3 to 6 mo.	1	1	..	..	..	1
6 to 12 mo.	4	..	..	..	..	..
More than 1 yr.	7	3	..	1	3	..
Total—30.	14	7	0	3	3	3
	47%	23%		10%	10%	10%
Group B						
Less than 3 mo.	4	..	..	2	..	..
3 to 6 mo.	..	1	..	..	2	..
6 to 12 mo.	1	..	1	..	..	..
More than 1 yr.	2	..	1	5	4	..
Total—23.	7	1	2	7	6	..
	30%	4%	9%	30%	26%	0%

the data were sufficient to lead to the conclusions presented in table 4 (group A). Complete failure to influence the disease was noted to be infrequent, occurring in 10 per cent, and not related to previous duration of the illness. Prolonged, complete or almost complete relief occurred commonly, also regardless of previous duration. Among the women with additional neurodermatitis, cure was found to be much less likely—43 versus 70 per cent—especially among those who had suffered previously for six or more months (table 4, group B). The last group of women also provided many more examples of recurrence following an initially favorable response and many patients who gained moderate improvement rather than really good results.

In general, the response to therapy was reasonably favorable. The recorded clinical notes give somewhat inadequate information as to the reasons for recurrence or failure, and yet two conclusions seem

justified: 1. When menopausal (climacteric) factors were clearly present in the history, two to four months of estrogenic treatment, when added to the more usual remedies, usually led to satisfactory results. 2. Persons with unsatisfactory results frequently displayed emotional and psychologic factors related to environmental phenomena which were not easily susceptible of modification.

COMMENT

Certain comments may be pertinent in reviewing the results of this survey of 83 patients with dermatitis of the suboccipital region. The disorder occurs chiefly in women, at all ages and with about the same frequency as neurodermatitis in general. There is perhaps a significant difference in a lower incidence in the group under 20 years of age and a higher incidence in the 30 to 40 year period. The relation to atopy seems neither more nor less evident than it is with neurodermatitis at other sites. When the condition is compared with other examples of neurodermatitis, the most evident variation is the increased incidence of association with abnormal menstruation. The nature of the abnormality cannot be stated with certainty, but it appears to be a diminution in estrogenic activity.

Having compared this process with neurodermatitis in general, it is reasonable for one to inquire what evidence is available to link it with that disorder. The clinical features are variable within certain limits and cannot be regarded as characteristic of a single form of neurodermatitis, such as lichen chronicus simplex. It cannot be assumed that the clinical variations occur only as results of trauma or treatment of a lichenified eruption. More often it seems that one is dealing with a more or less moist inflammatory papular eruption. It can be distinguished from psoriasis clinically, and sometimes with microscopic aid. Contact dermatitis may sometimes be superimposed, but usually this process can be excluded clinically, and in the cases studied the microscopic features were different from those of contact dermatitis. Seborrheic factors were not particularly evident in this series of cases and seemed not to be very significant when present. The microscopic features in 29 cases were characteristic of neurodermatitis, and it must be concluded that both the clinical and the microscopic features in this series of patients were those to be expected in neurodermatitis.

In general, the patients responded rather well to treatment, though it is difficult to develop particular enthusiasm for any single therapeutic regimen. In spite of widespread pessimistic views, it appears that good results are common, often regardless of long duration. The

results were less satisfactory when this eruption was accompanied by neurodermatitis at other sites; improvement was less likely to be really satisfactory, and recurrences were oftener observed. Estrogenic therapy is regarded as a valuable adjuvant when there are any other indications for its use. Emotional and psychologic factors seemed particularly important in those patients who did not improve. Treatment often included mild sedation and the use of some of the psychotherapeutic attempts of the nonpsychiatrist.

At the outset, this discussion avoided consideration of the question whether suboccipital dermatitis deserves analysis as a more or less separate entity. It appears to present many similarities to keratoderma climactericum. Each occurs almost entirely among women and frequently presents clinical features of subacute dermatitis as well as lichenification. Each disorder is commonly associated with evidence of estrogenic deficiency (or related endocrine factors) but is by no means limited to the climacteric age group. These endocrine factors appear to be more constantly evident among those women with palmar or plantar dermatitis, but in each group the therapeutic response is more likely to be favorable when estrogens are used. Psychologic and emotional factors seem clearly evident in both conditions, and to me both appear to be forms of neurodermatitis. If one regards neurodermatitis as always due to a complexity of causes rather than to a single agent or mechanism, then these two disorders (keratoderma climactericum and suboccipital dermatitis) may be looked at as differing from the other types of neurodermatitis chiefly by the importance of estrogenic deficiency in their pathogenesis.[7]

Why does neurodermatitis so frequently occur at the suboccipital fossa, and wherein lie the reasons for endocrine implications? Variations in an atopic element, such as specific allergic reactivity, seem incapable of explaining selectivity of site. Seborrheic or infectious factors appear not to be the answer. External influences seem to have no clear role unless one thinks of heat, perspiration or sebaceous activity; and, if these are localizing factors, they probably are activated by autonomic nervous mechanisms. One might hypothesize local differences in ionic metabolism, but these are not yet demonstrated and, if present, should be related either to local anatomic and structural factors (which have not been demonstrated) or, again, to vasomotor or other nervous control. Endocrine agents often manifest selectivity of site of action, usually influenced by anatomic structure, but sometimes by way of vasomotor phenomena. Psychologic and

7. Lynch, F. W.: Keratoderma Climactericum (Haxthausen), Arch. Dermat. & Syph. **42**:270 (Sept.) 1943.

emotional disturbance often influences the site of disturbed function, probably by use of the autonomic system, but this theory of the mechanism needs much elaboration.

CONCLUSION

The analysis of a series of 83 cases of suboccipital dermatitis has provided evidence suggesting that this disease is a form of neurodermatitis, differing from other forms not only in the site involved but also in frequent association with estrogenic abnormality and with psychologic and emotional factors, which may possibly influence the selection of site. I am incapable of describing the mechanism involved but can only call attention to the frequency of incidence of nuchal feelings of tension in women at the climacteric, the less known fact that the nuchal region is a zone of erotic significance in certain lower animals, such as the cat, and the well known fact that many incidents which lead to psychologic dissatisfaction are said to give one a "pain in the neck."

1466 Lowry Medical Arts Building (2).

ASSOCIATION OF PROGRESSIVE (MALIGNANT) EXOPHTHALMOS AND LOCALIZED MYXEDEMA

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AND
EDGAR B. JOHNWICK, M.D.
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IT IS GENERALLY accepted that localized myxedema occurs in conjunction with toxic diffuse goiter (Graves's disease) and often follows surgical removal of a thyrotoxic gland. A parallel situation exists with progressive (malignant) exophthalmos. The development, progress and duration of localized myxedema so strikingly simulates the course of progressive exophthalmos that one must accept as tenable the supposition that these two conditions are allied manifestations of the same underlying abnormally.

OPHTHALMIC COMPONENT OF TOXIC DIFFUSE GOITER

It is now recognized that there exist both a classic type and a special ophthalmopathic[1] variety of ocular change in association with toxic diffuse goiter. Ocular proptosis, an integral part of the syndrome comprising typical toxic diffuse goiter, may progress to a severer and more serious variant known as malignant exophthalmos. In most instances this development follows surgical removal of a thyrotoxic gland.

Since the demonstration by Loeb and Bassett[2] of an extract with thyrotropic quality from the anterior lobe of the pituitary gland, other extracts have been prepared which, when injected, produce changes similar to those found in the thyroid gland of toxic diffuse goiter, after which development the colloid material disappears, the epithelium becomes hyperplastic, and the alveolar cavities collapse. Signs of hyper-

From the Department of Dermatology and Syphilology, University of Michigan Medical School.

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 26, 1948.

This article was accepted for the August issue, a special number dedicated to Dr. Udo Julius Wile, but was omitted from that issue for technical reasons.

1. Means, J. H.: The Nature of Graves' Disease, with Special Reference to Its Ophthalmic Component, Am. J. M. Sc. **207**:1 (Jan.) 1944.

2. Loeb, L., and Bassett, R. B.: Comparison of Effects of Various Preparations of Anterior Pituitary Gland on Thyroid of Guinea Pig, Proc. Soc. Exper. Biol. & Med. **27**:490 (March) 1930.

thyroidism, such as increased heart rate, rise in metabolic rate, increased susceptibility to oxygen want, decreased iodine in the gland, increased iodine in the blood and exophthalmos [3] occur. It is also known that exophthalmos is not produced by the administration of the thyroid hormone to animals, nor is the gland of toxic diffuse goiter any more toxic when ingested than is a normal gland.

Whether the thyroid-stimulating hormone is the same as the exophthalmos hormone seems to have been answered by Albert,[4] who found, after injecting derivatives obtained from the anterior lobe of the pituitary gland of the sheep into the Atlantic minnow, that an exophthalmic factor was present which paralleled the action of the thyrotropic fraction qualitatively and quantitatively, whereas other fractions were ineffective in producing proptosis, even though they were employed in much greater dosage. Several investigators [5] showed that exophthalmos, experimentally produced by the administration of thyrotropic hormone, was much severer if the animals had previously been thyroidectomized, these observations upholding the theory that the thyroid-stimulating hormone is the cause of exophthalmos and that ablation of the thyroid gland enhances the effect of the hormone.

Friedgood showed that the thyroid gland of guinea pigs responded at first to the thyrotropic hormone by an increased metabolic rate and glandular hyperplasia but later became refractory even though the amount of thyroid-stimulating hormone given was increased. During the refractory stage the glandular hyperplasia disappeared and exophthalmos began to appear. The proptosis became most prominent during the refractory phase.[5b] This refractoriness of the thyroid gland to the thyroid-stimulating hormone was shown by Collip and Anderson to be due to an inhibiting substance (antihormone) which they found in the serum of treated animals.[6]

That the secretion of the thyroid gland, probably thyroxin or a thyroxin-like substance, in turn modifies the thyroid-stimulating hor-

3. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945, p. 726.

4. Albert, A.: The Experimental Production of Exophthalmos in Fundulus by Means of Anterior Pituitary Extracts, Endocrinology **37**:389 (Dec.) 1945.

5. (*a*) Marine, D., and Rosen, S. H.: Exophthalmos in Thyroidectomized Guinea Pigs by Thyrotropic Substance of Anterior Pituitary and Mechanism Involved, Proc. Soc. Exper. Biol. & Med. **30**:901 (April) 1933. (*b*) Friedgood, H. B.: Experimental Exophthalmos and Hyperthyroidism in Guinea Pigs: Clinical Course and Pathology, Bull. Johns Hopkins Hosp. **54**:48 (Jan.) 1934. (*c*) Smelser, G. K.: Experimental Production of Exophthalmos Resembling That Found in Graves' Disease, Proc. Soc. Exper. Biol. & Med. **35**:128 (Oct.) 1936.

6. Collip, J. B., and Anderson, E. M.: Production of Serum Inhibitory to Thyrotropic Hormone, Lancet **1**:76 (Jan. 13) 1934.

mone was shown by the work of Rawson, Sterne and Aub,[7] who demonstrated that if the thyroid-stimulating hormone is mixed as a substrate with cultures of thyroid cells it loses its physiologic activity. This loss is due to inactivation, since activity can be restored by reducing agents. Rawson, Graham and Riddell[8] further showed that thyrotoxic goiter cells inactivate twice as much thyroid-stimulating hormone as do normal thyroid cells. In progressive exophthalmos, unheated urine contains large quantities of active thyrotropic hormone. In progressive exophthalmos there is a total of active or inactive

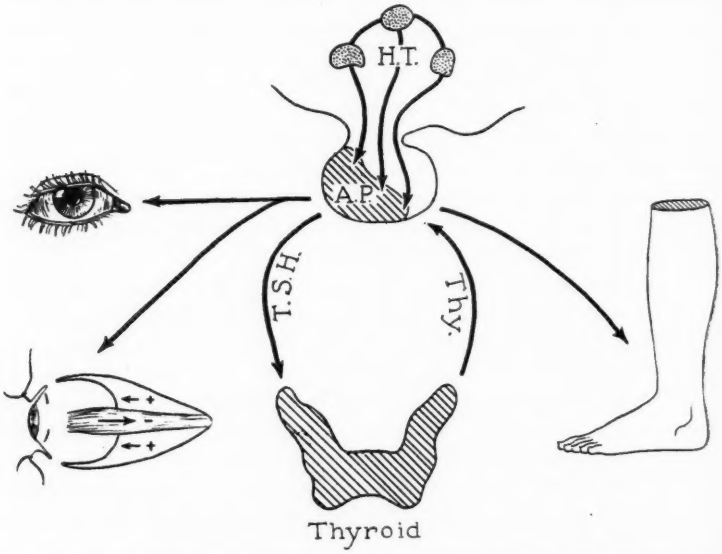

Fig. 1.—Schematic representation of the pituitary-thyroid axis described by Salter[13] and modified by Means.[1] *H.T.* represents the hypothalamus; *A.P.*, the anterior lobe of the pituitary gland, *T.S.H.*, the thyroid-stimulating hormone, and *Thy.*, the thyroxin secreted by the thyroid gland cells. A normal leg and eye are shown. The balance between the push of the retrobulbar contents and the pull of the eye muscles is also illustrated. The arrow from *A.P.* to the thyroid gland to the anterior lobe of the pituitary gland represents normal amounts of the secretion of thyroxin which inhibits secretion by the anterior lobe of the pituitary gland. The arrows from *A.P.* to the eye and leg are to illustrate the effects of the thyroid-stimulating hormone on these normal structures.

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7. Rawson, R. W.; Sterne, G. D., and Aub, J. C.: Physiological Reactions of Thyroid-Stimulating Hormone of Pituitary: Its Inactivation by Exposure to Thyroid Tissue in Vitro, Endocrinology **30**:240 (Feb.) 1942.

8. Rawson, R. W.; Graham, R. M., and Riddell, C. B.: Physiological Reactions of Thyroid Stimulating Hormone of Pituitary: Effect of Normal and Pathological Human Thyroid Tissues on Activity of Thyroid Stimulating Hormone, Ann. Int. Med. **19**:405 (Sept.) 1943.

thyroid-stimulating hormone greater than that in the urine of a person with a normal gland.[9] Rawson concluded that in toxic diffuse goiter the pituitary gland overacts in regard to the secretion of thyroid-stimulating hormone. In toxic diffuse goiter thyroid-stimulating hormone is inactivated, but in ophthalmopathic toxic diffuse goiter either a large proportion of the thyroid cells have been surgically removed or they cannot rise to the stimulus, and hence most of the thyroid-stimulating hormone remains active. Depression of activity of

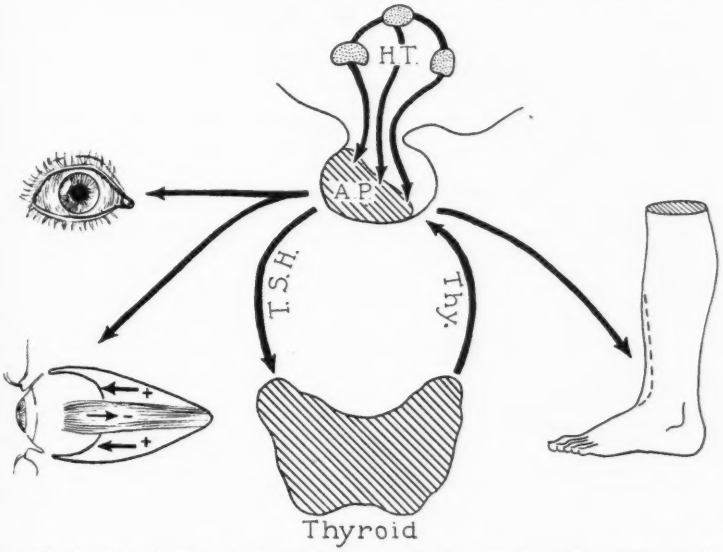

Fig. 2.—The pituitary-thyroid axis now shows increased activity of the whole system due to toxic diffuse goiter, with hyperplasia of the thyroid gland, exophthalmos and edema of the leg. It is believed that the stimulus which starts the cycle of increased secretion arises from shock, worry, responsibility or previous illness, for example, in an already susceptible person.[1] The hypothalamus increases its stimulus to the pituitary gland. This action causes increased thyroid-stimulating hormone to be secreted, which secreting in turn causes thyroid glandular hyperplasia and edema, hypertrophy of the muscle and retraction of the lids of the eye, these developments producing exophthalmos. Edema of the leg occurs. The thyroid gland secretes more thyroxin in an attempt to neutralize the thyroid-stimulating hormone. The balance now is at higher or accelerated level.

the thyroid-stimulating hormone in rat pituitary secretion to less than 5 per cent of normal by administration of thyroid was shown by Purves and Griesbach.[10] Although it was pointed out that progressive exoph-

9. Rawson, R. W.: Personal communication to the author; cited by Means.[1]

10. Purves, H. D., and Griesbach, W. E.: Effect of Thyroid Administration on Thyrotropic Activity of Rat Pituitary, Endocrinology **39**:274 (Oct.) 1946.

thalmos is relatively more frequent in men,[11] there is controversy as to the role of the gonads in its production.[12] The effect of the secretion of each gland on the other has been referred to as the pituitary-thyroid axis.[13]

The changes produced in the orbit by the thyroid-stimulating hormone are an actual increase in volume of the retrobulbar structures, due to edema and cellular infiltration. The weakness of the extrinsic ocular muscles, due to edema and cellular infiltration, and the pressure

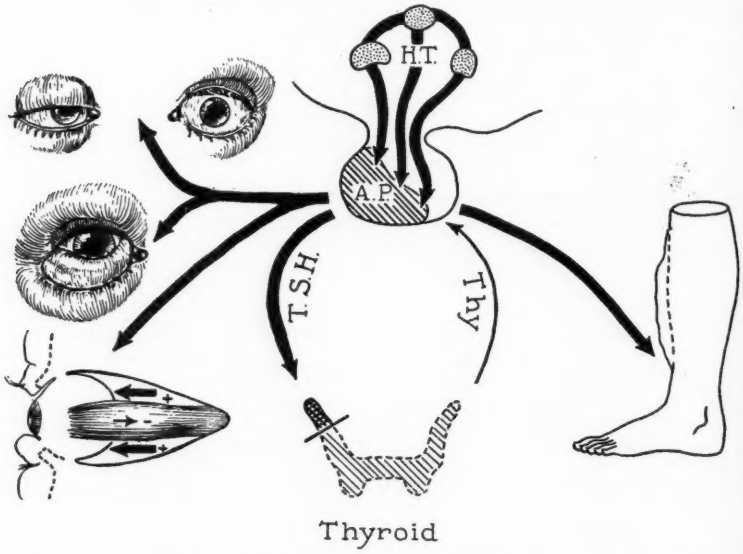

Fig. 3.—Schematic representation of the pituitary-thyroid axis in progressive exophthalmos. The drive of the thyroid-stimulating hormone on other structures as a result of hypothalamic stimulation is now uninhibited because of thyroidectomy or atrophy and consequent decided reduction of the thyroid gland's neutralizing secretion of thyroxin. The eyes show exophthalmos, and the lids are retracted or ptotic. Chemosis is present, and edema of the periorbital tissue is prominent. These signs may be unilateral. Weakness of the rectus and oblique muscles of the eye and of the levatores palpebrarum may be present, and divergent or convergent strabismus may be seen, with or without ptosis. There is hypertrophy of the eye muscles, which become weak, and proptosis is more appreciable as a result of the push of edematous structures behind the eye and the pressure from swollen muscles. Localized edema of the legs is not infrequently present.

11. Marine, D.: Studies on Pathological Physiology of Exophthalmos of Graves' Disease, Ann. Int. Med. **12**:443 (Oct.) 1938.

12. Dobyns, B. M.: Studies on Exophthalmos Produced by Thyrotropic Hormone: I. A Study of Exophthalmos Produced by Various Thyrotropic Hormones and the Influence of the Testes on the Exophthalmos, Surg., Gynec. & Obst. **82**:290 (March) 1946.

13. Salter, W. T.: The Endocrine Function of Iodine, Cambridge, Mass., Harvard University Press, 1940.

exerted by the swollen retrobulbar contents lead to anterior displacement of the globe.[14] An actual increase in muscle fat has also been demonstrated [15] and may likewise be of some importance. Administration of the thyroid-stimulating hormone to animals produces alterations in cardiac and skeletal muscle fibers [16] closely akin to those found in the corresponding muscles of human beings with toxic diffuse goiter, which observation may account in some measure for the myasthenia associated with toxic diffuse goiter.[17] Figures 1, 2 and 3 graphically illustrate the pituitary-thyroid relationship.

The clinical picture of progressive exophthalmos is an extremely variable one. Means [18] emphasized that classic exophthalmos may later become progressive and stated the belief that such severe subsequent changes should probably be regarded as a continuous process rather than a special type of toxic diffuse goiter. The staring facies and widening of the palpebral fissure, with exposure of the sclera of the eye above the iris, are pathognomonic of toxic diffuse goiter. In progressive exophthalmos, bulging of the lids, chemosis of the conjunctiva, muscle weakness and palsies and limitation of ocular movements (especially those upward), as well as exophthalmos, are characteristic. Such changes are not infrequently unilateral. The onset of progressive exophthalmos may on occasion be abrupt, though more often it is gradual. On rare occasions the ocular disorder becomes so pronounced that orbital decompression becomes necessary.[19] In rare cases, in which the implications of severe and progressive exophthalmos have not been promptly recog-

14. (*a*) Moore, R. F.: Exophthalmos and Limitation of Eye Movements of Graves' Disease, Lancet **2**:701 (Oct. 2) 1920. (*b*) Thomson, E. S.: Orbital Edema in Exophthalmic Goiter, Am. J. Ophth. **7**:27 (Jan.) 1924. (*c*) Smelser, G. K.: Histology of Orbital and Other Fat Tissue Deposits in Animals with Experimentally Produced Exophthalmos, Am. J. Path. **15**:341 (May) 1939. (*d*) Paulson, D. L.: Experimental Ophthalmos and Muscle Degeneration Induced by Thyrotropic Hormone, Proc. Staff Meet., Mayo Clin. **14**:828 (Dec. 27) 1939. (*e*) Mainini, C. G.: Exophthalmometric Measurements in Patients with Thyroid Diseases with Some Discussion of Their Significance, Ann. Int. Med. **16**:415 (March) 1942.

15. Paulson.[14d] Mainini.[14e]

16. Dobyns, B. M.: Studies on Exophthalmos Produced by Thyrotropic Hormone: II. Changes Induced in Various Tissues and Organs (Including the Orbit) by Thyrotropic Hormone and Their Relationship to Exophthalmos, Surg., Gynec. & Obst. **82**:609 (May) 1946; III. Further Study of Changes Induced in Fat by Thyrotropic Hormone (Tissue Reactions Associated with Exophthalmos), ibid. **82**:717 (June) 1946.

17. Footnote deleted.

18. Means, J. H.: Hyperophthalmopathic Graves' Disease, Ann. Int. Med. **23**:779 (Nov.) 1945.

19. Naffziger, H. C.: Progressive Exophthalmos Following Thyroidectomy: Its Pathology and Treatment Tr. Am S. A. **49**:168, 1931.

nized, ulceration of the conjunctiva, with subsequent ophthalmitis, has occurred and enucleation has been necessary. There is a definite tendency for activity of the process to be self limited to a few months or years, but the exophthalmos seldom completely subsides.[1]

LOCALIZED MYXEDEMATOUS COMPONENT OF TOXIC DIFFUSE GOITER

The term localized myxedema is especially incongruous and paradoxic. It implies a cutaneous myxedematous disorder fundamentally related to hypothyroidism, despite the fact that most examples have occurred in conjunction with toxic diffuse goiter.

Pillsbury and Stokes [20] recorded the case of a woman who had a subtotal thyroidectomy for toxic diffuse goiter. She later presented the signs and symptoms of generalized myxedema and was relieved by the ingestion of desiccated thyroid gland. After she discontinued medication both generalized myxedema and infiltrated plaques of localized myxedema developed over the tibias. Further administration of desiccated thyroid afforded relief from the signs and symptoms of constitutional myxedema but did not alter the status of the pretibial plaques. The failure in this case, as well as in others, of long-continued and adequate medication with desiccated thyroid to influence localized myxedema is strong presumptive evidence that this disorder and constitutional myxedema are etiologically unrelated. The thyroid-stimulating hormone, which is so closely identified with the cause of progressive exophthalmos, may well be the fundamental factor in production of the lesions of localized myxedema (fig. 3).

The microscopic features of localized myxedema are demonstrable in all clinically recognized lesions. There are usually edema, homogenization, fraying and splintering of the dermal connective tissue elements. Those changes probably precede myxedematous degeneration of the collagen, which eventuates in the presence of variable amounts of mucin in the thickened cutis. The latter feature relates localized myxedema pathologically to generalized myxedema. The occurrence of stellate cells, probably immature connective tissue cells,[20] scattered throughout the mucin has been described, although this is apparently not a consistent observation. Flattening of the epidermis and obliteration of the rete ridges, if present, are secondary to the underlying dermal edema. Mucin is found microscopically in the dermis in both constitutional and localized myxedema, although in the latter disorder huge quantities of the material are usually apparent when the condition has reached the clinical horizon.

The lesions of localized myxedema are roughly oval indurated yellowish brown plaques, occasionally as large and thick as a man's

20. Pillsbury, D. M., and Stokes, J. H.: Circumscribed Myxedema of the Skin, Arch. Dermat. & Syph. **24**:255 (Aug.) 1931.

hand, which do not pit on pressure and seldom exceed three or four. Their surface has at times the appearance of pigskin and is less often studded with dome-shaped papules. Mild itching and burning of the involved skin are sometimes present. Such lesions are usually bilateral and limited to the lower anterolateral surface of the legs. Nodular infiltrations occurring on the face, arms, back and scrotum have been described in the literature under the same title.[21] Many patients with localized myxedema confined to the legs have had antecedent and transient pitting edema of the lower extremities. This, however, is not an infrequent accompaniment of toxic diffuse goiter.[1] Systemic treatment has little or no appreciable effect on the lesions of localized myxedema. They may show evidence of spontaneous regression after a few months or years, thus paralleling the usual career of progressive exophthalmos. In at least 1 case the plaques were surgically removed for cosmetic reasons.

PROGRESSIVE EXOPHTHALMOS AND LOCALIZED MYXEDEMA AS ALLIED MANIFESTATIONS OF THE SAME UNDERLYING DISORDER

Progressive exophthalmos is not frequently encountered, and localized myxedema is a dermatologic rarity; yet we have been able to find 5 recorded examples in which patients had the two disorders simultaneously.[22] In 1 of these, reported by Netherton,[22c] the localized myxedema cleared after cauterization of the anterior lobe of the pituitary gland.[23] Other reports have implied, in title or otherwise, coexistence of the two diseases but have devoted their discussion exclusively to one or the other component. It seems probable that if all patients with progressive exophthalmos were examined for localized myxedema, or the reverse, an ever increasing number of persons who had these disorders concurrently would be observed.

In a majority of cases, toxic diffuse goiter, with one or more subsequent thyroidectomies, precedes the development of either progressive exophthalmos or localized myxedema. Occasional exceptions to this rule may be explained by a lack of hyperplasia of the thyroid gland or its rapid atrophy. The former may be due to an inability of the thyroid gland to respond to the thyroid-stimulating hormone, and the latter, to exhaustion. The pituitary-thyroid axis is then altered either by the surgical removal of the thyroid gland, with a resultant excess of unneutralized thyroid-stimulating hormone or by the situation in

21. (*a*) Pillsbury and Stokes.[20] (*b*) O'Leary, P. A.: Localized Solid Edema of the Extremities in Association with Exophthalmic Goiter, Arch. Dermat. & Syph. **21**:57 (Jan.) 1930.

22. (*a*) Pillsbury and Stokes.[20] (*b*) Ingram, J. T.: Circumscribed Myxedema Associated with Hyperthyroidism, Brit. J. Dermat. **45**:19 (Jan.) 1933. (*c*) Netherton, E. W.: Localized Myxedema: Case Presentation, Arch. Dermat. & Syph. **48**:123 (July) 1943.

23. Netherton, E. W.: Personal communication to the authors.

which the thyroid gland cannot liberate enough thyroxin to inactivate this secretion (fig. 3).

The thyroid-stimulating hormone is known to be a potent factor in the formation of edema. Its antagonist, thyroxin, possesses diuretic and dehydrating properties. The edema-producing quality of active thyroid-stimulating hormone no doubt contributes much to the evolution of progressive exophthalmos. It may have the same effect in initiating localized myxedema.

It has been recognized that the lesions of localized myxedema may increase in size after thyroidectomy. This development is analogous in those patients with ophthalmopathic toxic diffuse goiter to the progression of exophthalmos following thyroidectomy. Collagen, from which mucin is derived,[24] is not present in the orbital contents in appreciable quantity, though it occurs abundantly in the skin. This fact probably accounts for the occasional huge deposits of mucin in localized myxedema and its apparent absence in the orbits of progressive exophthalmos, despite an otherwise seemingly close relationship.

The clinical course pursued by both localized myxedema and progressive exophthalmos is practically identical. The onset may be simultaneous. Both appear most often after thyroidectomy for toxic diffuse goiter. Both persist for months or years, but activity is definitely self limited. Spontaneous regression, inconstant and unpredictable, has been observed with each disorder. That such a phenomenon occurs suggests a refractory state, then a recession of lesions in man similar to that noted by Friedgood in animals,[6b] possibly due to the formation of an antihormone, such as that suggested by Collip and Anderson,[6] which neutralizes the thyroid-stimulating hormone.

Plummer and Wilder,[24a] in a symposium on exophthalmos fourteen years ago, made the following observations, which anticipated in some measure the correlation of progressive exophthalmos and localized myxedema:

> Why should the external rectus muscles become swollen and hardened, and enlarge to several times their normal thickness? Why should edema develop in the lids when it was absent in the stage featured by a high basal metabolic rate? The evidence from the laboratory suggests that overfunction of the anterior lobe of the pituitary body may play a part in the production of this abnormality . . . . The edematous contents of the orbit are comparable in some respects to localized subcutaneous areas of mucinous edema, which are found in rare cases of exophthalmic goiter, particularly after thyroidectomy.

The administration of thyroid extract is not often productive of notable results with either progressive exophthalmos or localized

24. MacLeod, J. M. H., and Muende, I.: Practical Handbook of the Pathology of the Skin, ed. 3, New York, Paul B. Hoeber, Inc., 1946.

24a. Plummer, W. A., and Wilder, R. M.: Etiology of Exophthalmos: Constitutional Factors, with Particular Reference to Exophthalmic Goiter, Tr. Am. Acad. Ophth. **39**:41, 1934.

myxedema. Its apparent benefit in some cases may have been due to spontaneous improvement. Thiouracil, which interferes with the synthesis of thyroxin by the thyroid gland, produces what has been aptly termed a medical thyroidectomy. Because the thyroid-stimulating hormone factor is not only uninhibited but may increase as a response to the failure of function of the thyroid gland, medication with thiouracil has not proved effective and may be harmful. Irradiation of the pituitary gland in toxic diffuse goiter holds some promise.[25]

In patients with toxic diffuse goiter and ophthalmic changes suggestive of progression, thyroidectomy should be avoided. Because these patients may also acquire localized myxedema, the same contraindication for operation should hold for the two conditions.

REPORT OF CASES

CASE 1.—C. C., a white man aged 50, was admitted to the ophthalmology service at the University Hospital, Aug. 7, 1947, complaining of bleeding on urination, as well as protrusion of the eyes. His ocular difficulties had begun in June 1947 with photophobia and conjunctivitis, which had become severer. His past health had always been good except as noted previously.

Physical examination showed bilateral eversion of the inferior bulbar and palpebral conjunctivas, with extreme chemosis, decided protrusion of the globes (fig. 4 *D*) and exophthalmometer readings of 25 mm. for the right eye and 27 mm. for the left eye. The patient was referred to the department of urology and found to have a carcinoma of the urinary bladder, for which a successful radical operation was subsequently performed.

Laboratory studies revealed a basal metabolic rate of —2 per cent and plasma cholesterol, 126 mg. per hundred cubic centimeters. A diagnosis of progressive exophthalmos was made, and the patient started the ingestion of 1 grain (0.06 Gm.) of thyroid extract each day. Numerous subsequent examinations showed the basal metabolic rate to be consistently in the neighborhood of —2 per cent. There was slow improvement of the progressive exophthalmos, for the exophthalmometer reading in March 1948 was 17 mm. for each eye. The patient had continued the ingestion of thyroid, although the amount had not been consistent, varying from 1 to 3 grains (0.19 Gm.) each day.

CASE 2.—L. S., a white woman aged 52, was admitted to the surgical service of the University Hospital on April 4, 1941. She had been as well as was usual until July 1940, when she had first noticed slight protrusion of her eyes, photophobia, myasthenia, intolerance to heat and loss of weight. During subsequent months these manifestations had become more pronounced, and at the time of admission she had lost 40 pounds (18.1 Kg.). Her past health otherwise had been good.

Significant ocular findings were bilateral exophthalmos, with exophthalmometer readings of 23.5 mm. for the right eye and 25 mm. for the left eye and some lid lag. The thyroid gland was palpable and firm but not nodular. The skin was moist and warm, and the examining physician made a diagnosis of exophthalmic goiter. Significant laboratory findings were a basal metabolic rate of +49 per cent and plasma cholesterol of 194 mg. per hundred cubic centimeters. The patient received strong iodine solution U. S. P. (Lugol's solution) by mouth

25. Thompson, W. O.: What's New in Endocrinology, J. A. M. A. **136**:314 (Jan. 31) 1948.

for three weeks, at the end of which time the basal metabolic rate was +2 per cent, and a subtotal thyroidectomy was performed. Microscopic examination of the thyroid gland showed pathologic changes of toxic diffuse goiter. The patient's convalescence was uneventful, and she was discharged on May 3, 1941.

The patient returned to the hospital on June 24, 1941, and stated that she felt much improved subjectively. Exophthalmometer readings, however, were 29 mm. for the right eye and 29 mm. for the left eye, and the ophthalmologist diagnosed progressive exophthalmos. Her basal metabolic rate was —2 per cent. At about this time the department of gynecology performed a dilation, curettage and conization of the cervix because of cystic cervicitis and polypoid glandular erosion of the cervix. The examining physician noted "an area of brawny induration on the medial aspect of the left shin" but did not have the patient seen by a dermatologist. Because of further progression of the exophthalmos, intracranial decompression of the orbits was advised and subsequently performed by the neurosurgeon in two stages between July 1 and July 15. Pathologic examination of orbital

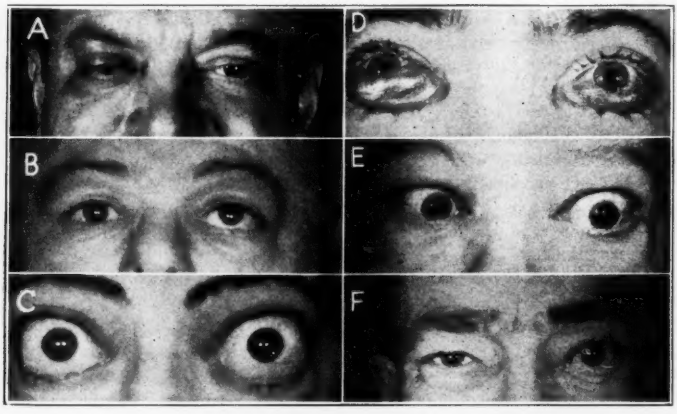

Fig. 4.—*A* (case 6), showing ptosis of both lids, more pronounced on the right, and muscular palsy. The photograph was taken in 1948, thirteen years after the onset of toxic diffuse goiter and two and one-half years after a third subtotal thyroidectomy. *B* (case 3), showing pronounced exophthalmos on the left side and swelling of the periorbital tissues. Exophthalmos is decided but deceiving because there is no retraction of the lid. *C* (case 4), illustrating to good advantage the widened palpebral fissure and exposure of the sclera of the eye above the iris. *D* (case 1), showing severe conjunctival chemosis, often an early manifestation of progressive exophthalmos. *E*, the widened palpebral fissure and muscle palsy of progressive exophthalmos. *F*, unilateral lid ptosis and exophthalmos and edema of periorbital tissues, more evident on the left side.

muscle showed variation in staining of the muscle fibers and heavy lymphocytic infiltration (fig. 5 *A* and *B*). Special staining procedures carried out at a later date revealed that one of two specimens of muscle contained mucin in small quantities.

The patient was not seen again until December 1946, at which time she was examined only by the ophthalmologist, who noted that she had been feeling well and that her exophthalmos had definitely regressed without medication during the interim but that there was weakness of the internal rectus of the right eye and lid lag of the left eye. Exophthalmometer readings were 19.25 mm. for the right

eye and 24.5 mm. for the left eye. There was no further notation about the lesion on the leg, which may well have been localized myxedema.

CASE 3.—H. F., a white woman aged 41, was admitted as an outpatient to the ophthalmology service of the University Hospital on Oct. 22, 1945. Four years previously she had undergone a thyroidectomy elsewhere because of

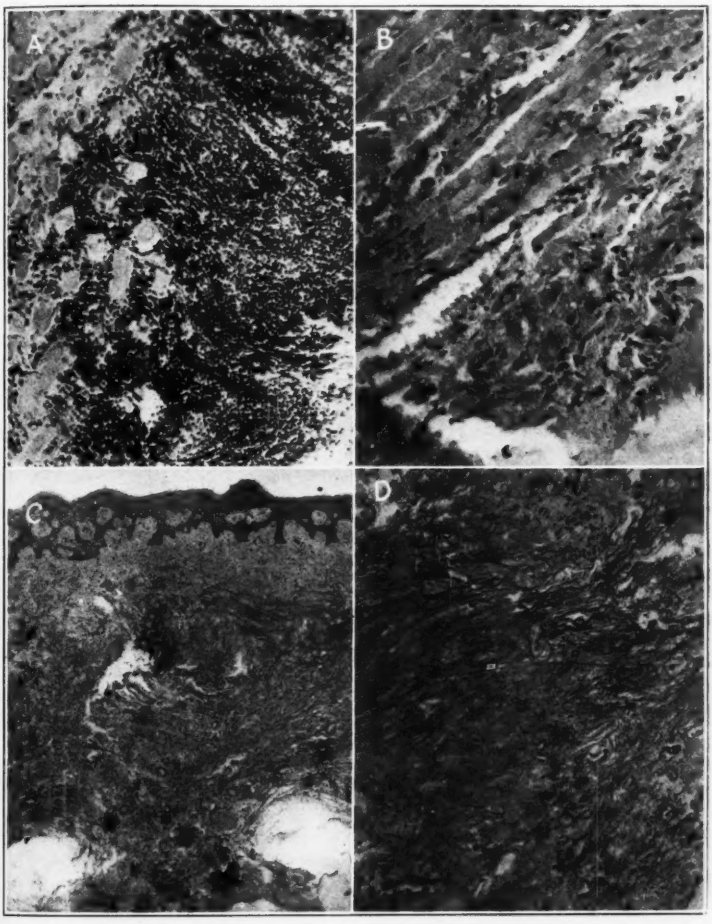

Fig. 5.—*A*, high power view of orbital muscle obtained at operation in case 2, showing the heavy lymphocytic infiltration which obscures the muscle bundles in most areas. *B*, high power view of another section of orbital muscle from the patient in case 2. A lymphocytic infiltrate is apparent, although it is not as pronounced as in *A*. There is also some edema. *C*, low power view of a microscopic section from one of the lesions of localized myxedema in case 5. Large quantities of mucin are present in the dermis. The microscopic features of the lesions of the leg in case 6 were almost identical. *D*, high power view of the mucin observed in case 5. A few sweat gland tubules can be seen.

hyperthyroidism with typical symptoms. Her basal metabolic rate at that time was said to have been + 56 per cent. Thyrotoxic symptoms were completely relieved, and the patient felt unusually well until April 1945, when she first noticed bilateral painless swelling of the lids, proptosis and diplopia, which persisted. Her past health, except as noted, had always been excellent.

Examination at the time of admission disclosed bilateral ocular proptosis, with exophthalmometer readings of 15 mm. for the right eye and 21 mm. for the left eye, with limitation of abduction in the left eye. At this time the basal metabolic rate was + 10 per cent. There were no other significant findings. The patient was placed on 15 drops of strong iodine solution and 1½ grains (0.09 Gm.) of desiccated thyroid a day. When she returned in one month the basal metabolic rate was + 4 per cent and the exophthalmometer readings 18 mm. for the right eye and 23 mm. for the left eye. Despite cessation of treatment with the strong iodine solution and an increase in the dose of thyroid extract to 4 grains (0.26 Gm.) each day, which subsequently had to be reduced to 3 grains because of thyrotoxic symptoms, there was continued progression of the exophthalmos. Readings on March 21, 1946, were 22 mm. for the right eye and 24 mm. for the left eye, with appreciable paresis of the left inferior oblique muscle and weakness in abduction of the left eye (fig. 4*B*). The basal metabolic rate at this time was plus 30 per cent. The endocrinologist advised roentgen irradiation of the pituitary gland, but the patient did not return for further observation or treatment.

CASE 4.—B. F., a white woman aged 35, was admitted as an outpatient to the ophthalmology service of the University Hospital on Feb. 14, 1945. In March 1942 she had had symptoms of hyperthyroidism and slight exophthalmos, with a basal metabolic rate of + 59 per cent. A thyroidectomy was done elsewhere in April 1942, after which the patient was relieved of most of her symptoms but did not notice any change in the proptosis. The basal metabolic rate in December 1942 was + 36 per cent. Because of recurrent symptoms of hyperthyroidism, another thyroidectomy was performed in November 1944, at which time the basal metabolic rate was + 4 per cent, and the exophthalmos subsequently became much worse.

Physical examination at the time of admission showed pronounced bilateral conjunctival hyperemia and chemosis over the lower half of each globe and palpable fusiform enlargement of the extraocular muscles (fig. 4*C*). There were no other significant findings. The basal metabolic rate was — 6 per cent. Despite continued administration of dessicated thyroid in adequate dosage, the exophthalmos was progressive, and in August 1945 the basal metabolic rate was + 5 per cent, and the exophthalmometer readings, 32 mm. for each eye. At about this time the patient decided to go elsewhere for further observation and treatment.

CASE 5.—R. Y., a white man aged 45, was admitted to the medical service of the University Hospital on Feb. 18, 1935, complaining of intolerance to heat, nervousiness, irritability, incresaed appetite and loss of 16 pounds (7.3 Kg.) which had been sustained since the onset of symptoms in December 1934. The patient's health in the past had been good.

The examining physician found that the thyroid gland was palpable only at the isthmus and noted that this was deep in the suprasternal notch. There was slight cardiac enlargement, with a gallop rhythm heard best at the apex, and the blood pressure was 170 systolic and 90 diastolic. The rest of the physical examination showed normal conditions.

Complete laboratory studies revealed a basal metabolic rate of + 45 per cent, which two days later was plus 40 per cent, but no other significant findings. A diagnosis of toxic diffuse goiter was made and the patient placed on treatment

with strong iodine solution, which had to be discontinued after three weeks because of his intolerance to the medication.

On March 12, 1935, the basal metabolic rate was reported as + 28 per cent, and two days later a subtotal thyroidectomy was performed. The pathologist reported the tissue as that of iodized toxic diffuse goiter. After an uneventful convalescence the patient was discharged on March 25. In May 1936 he returned, stating that he had felt much improved after the operation but that he had recently noticed some protrusion of his eyes, as well as thickened areas on the lower portion of the legs. The ophthalmologist reported bilateral exophthalmos with slight lid lag and exophthalmometer readings of 22 mm. for each eye. On the anterior surface of each shin was a large, tawny, indurated plaque which extended to the lateral surface of the leg (fig. 6*A*) and had the clinical features

Fig. 6.—*A* (case 5), the large plaque of localized myxedema on the lower right leg, shown to good advantage. There was a similar lesion on the left leg. *B*, the localized myxedema of case 6, five years after it had first appeared. There had been very considerable regression of the lesions during this period.

of localized myxedema. The basal metabolic rate was + 3 per cent, and the plasma cholesterol, 127 mg. per hundred cubic centimeters. Two years later, in April 1938, the patient returned to the hospital having had no treatment during the interim. Exophthalmometer readings were 23 mm. for the right eye and 23.5 mm. for the left eye, and there was persistence of the previously noted lid lag as well as slight limitation of abduction. The basal metabolic rate was + 6 per cent. Microscopic examination of a biopsy specimen from the lesion on the leg showed the epidermis to be atrophic, overlying a corium in which there was almost complete mucinous degeneration of the connective tissue elements (fig. 5*C* and *D*).

The patient was not seen again for eight years, after which time he returned to the hospital and died within forty-eight hours, having had what apparently

was a cerebrovascular accident, although permission for an autopsy could not be obtained. The exophthalmos was still pronounced, but the localized myxedema had regressed considerably, there still being some evidence of the disorder on the left shin.

Case 6.—D. S., a white man aged 34, was admitted to the surgical service of the University Hospital on Oct. 23, 1945, complaining of recurrent enlargement of the thyroid gland. In 1935, he had had symptoms of severe hyperthyroidism, including exophthalmos. After subtotal thyroidectomy elsewhere, there had been considerable improvement for six months, after which time the symptoms recurred and a second operation was performed, with further removal of thyroid tissue. The patient subsequently felt well for several years, and the exophthalmos partially regressed. In the spring of 1943 the patient noticed a nodule in the center of the thyroidectomy scar, together with symptoms of recurrent hyperthyroidism, including nervousness, ease of fatigue, palpitation, increased sweating and tremor of the hands. At about the same time he became aware of a small, flesh-colored papule, which was asymptomatic, on the anterior aspect of the right leg. During the next year and a half the patient's symptoms became severer and the lesion on the right leg increased in size and was accompanied with a similar one on the left shin. The patient's health in the past, except as noted previously, had always been good.

Physical examination at the time of admission revealed a large mass of thyroid tissue palpable above the old operative scar in the midline. There were appreciable bilateral exophthalmos, with exophthalmometer readings of 23 mm. for the right eye and 25 mm. for the left eye, and ptosis of both upper lids, more pronounced on the right. On the anterior aspect of each leg, extending from the ankle to within 6 inches (15 cm.) of the knee, were indurated yellowish brown plaques, the surface of each being studded with numerous papules and small nodules. The rest of the physical examination showed normal conditions.

Complete laboratory studies revealed a basal metabolic rate of — 15 per cent but no other significant findings. The endocrinologist made a diagnosis of thyrotropic exophthalmos and suggested the possibility of neoplastic change in a thyroid adenoma, while the dermatologic consultant described the lesions on the legs as those of localized myxedema. A third subtotal thyroidectomy was performed in November 1945. The pathologist reported adenocarcinoma of the thyroid gland, while microscopic examination of tissue from the lesion on the leg showed pronounced mucinous degeneration and edema of the corium, a picture interpreted as that of localized myxedema. High voltage roentgen therapy was administered to the thyroid region postoperatively.

Exophthalmometer readings on December 13 were 24 mm. for the right eye and 27 mm. for the left eye. The patient was discharged and advised by the endocrinologist to take 1½ grains of desiccated thyroid each day in an effort to avert further progression of an already severe exophthalmos. He returned to the hospital in April 1946, at which time his basal metabolic rate was —11 per cent and he had gained considerable weight and was feeling well. During subsequent months he continued the ingestion of thyroid extract and complained only of tiring easily. In July 1946, his basal metabolic rate was —7 per cent and in August 1947 —4 per cent. When examined most recently at the hospital on Feb. 20, 1948, the patient stated that he had felt better for the preceding few months than for the past several years. He had found that best results were obtained from 3 grains of thyroid extract each day. The exophthalmos had regressed considerably, but the ptosis was more decided (fig. 4*A*) and the lesions of localized myxedema were somewhat smaller (fig. 6*B*). There was no demonstrable recurrence of the thyroid carcinoma.

COMMENT

The belief that progressive exophthalmos and localized myxedema are coexistent far oftener than recorded is supported by the fact that 3 of 4 patients recently seen at the University Hospital have had both. The fourth patient had only localized myxedema. Cases 5 and 6 are examples of such association. Five cases records of localized myxedema found in the literature mentioned the concurrent existence of progressive exophthalmos as an incidental finding.[22] Dr. Frank C. Hoak and Dr. Eugene Hand have each presented a similar case.[26] If these are added to the 3 we have observed, a total of 8 patients are known to have had both.

The staring facies and widely retracted lids make the exophthalmos of toxic diffuse goiter strikingly apparent. If retraction of the lid disappears or is replaced by ptosis, or if chemosis occurs, the exophthalmos seems less severe, and yet the degree of exophthalmos may actually be as great or greater. This is illustrated by comparing the photographs of the patients in cases 4 and 1 (fig. 4*C* and 4*D*). Exophthalmos is more apparent and seems greater in the former than the latter patient, and yet exophthalmometer readings at the time the photographs were taken showed essentially the same degree of exophthalmos in the two.

Case 6 (fig. 4*A*) illustrates bilateral ptosis, edema and, on close inspection, muscle weakness. The patient shown in figure 4*F* had pronounced exophthalmos, obscured, however, by ptosis and periorbital edema. The unilateral character of the disorder is rather striking in in this instance. Figure 4*E* shows evidence of palsy of the muscle to good advantage, while figure 4*B* (case 3) illustrates the distended, discolored, periorbital tissues, a condition unilateral in this instance but which may be either unilateral or bilateral. A typical tawny plaque of localized myxedema in the usual location is shown in figure 6*A* (case 5), while figure 6*B* (case 6) illustrates the nodular, yet circumscribed, character of the lesions of the leg. It seems probable that one or the other component, usually localized myxedema, because of its location and innocuous character, is often unrecognized or minimized. Case 2 is a likely example.

With one exception, the cases presented here illustrate the importance of thyroidectomy in the development of progressive exophthalmos. It is worth noting that in case 1, in which progressive exophthalmos made its appearance without benefit of antecedent thyroidectomy, the response to medication with thyroid extract was good, while the results of similar

26. A patient with localized myxedema and hyperthyroidism presented by Dr. Frank C. Hoak at the Buffalo meeting of the Central States Dermatological Association, April 10, 1948, had progressive exophthalmos as well. Both phenomena appeared six months after the patient started medication with thiouracil. A few days later, Dr. Eugene Hand, of Saginaw, Mich., sent us photographs of one of his patients who exhibited both disorders after thyroidectomy for toxic diffuse goiter.

treatment in several of the other cases were equivocal. This observation would appear to be corroborative experimental evidence that thyroxin inactivates thyrotropin. All three examples of localized myxedema occurred after surgical removal of the thyroid gland. The patient in case 6 had three thyroidectomies but acquired progressive exophthalmos and localized myxedema after the second operation.

The numerous recorded determinations of basal metabolic rate do not reveal convincing metabolic evidence of hyperthyroidism or hypothyroidism at the time the localized myxedema or progressive exophthalmos developed, although toxic diffuse goiter preceded its onset in most instances. Neither are the plasma cholesterol levels definitely indicative, although those recorded, with one exception, were somewhat lower than normal.

A microscopic review of the pathologic material obtained from the orbits of several persons with progressive exophthalmos revealed edema of the muscles and retrobulbar fat, with an increase in muscle fat in some cases. There was round cell infiltration of variable degree in almost every case, and not infrequently this was concentrated in the vicinity of blood vessels. Degenerative muscular changes encountered included variation in staining power, loss of cross striations and areas of hyalinization and fragmentation. Special staining reactions revealed small quantities of mucin in 1 instance (case 2), this observation providing further evidence of the relations between localized myxedema and progressive exophthalmos. It was seldom possible to find all features fully developed in one specimen.

The microscopic examination of tissue from both patients with localized myxedema showed the characteristic microscopic features of this process.

In general, a careful review of the cases presented here lends support to the hypothesis that localized myxedema and progressive exophthalmos are probably allied manifestations of the same underlying disorder.

SUMMARY

1. Progressive exophthalmos, a severer and more serious variant of the ocular proptosis which is part of the syndrome comprising typical toxic diffuse goiter, develops in most instances after surgical removal of a toxic thyroid gland. Abundant experimental evidence has been presented within recent years to show that a thyroid-stimulating hormone elaborated by the anterior lobe of the pituitary gland is a major factor in the production of progressive exophthalmos.

2. Similarly, the lesions of localized myxedema, usually bilateral and limited to the lower anterolateral surface of the legs, are almost always associated with or preceded by clinical manifestations of toxic diffuse goiter, and thyroidectomy or thiouracil therapy usually initiates their onset.

3. The development, progress and duration of localized myxedema so strikingly simulates the course of progressive exophthalmos that one must accept as tenable the supposition that the two conditions are allied manifestations of the same underlying disorder and probably both due to an excess of thyroid-stimulating hormone.

4. The association of both progressive exophthalmos and localized myxedema in 3 of the 4 cases we have studied and in 7 other reported or known cases is further evidence that these two disorders are clinically related.

University Hospital.

ABSTRACT OF DISCUSSION

DR. EARL W. NETHERTON, Cleveland: We are indebted to Drs. Curtis, Cawley and Johnwick for this excellent paper. After a careful consideration of accumulated experimental and clinical data, Dr. Curtis and his collaborators have proposed the hypothesis that progressive exophthalmos and localized myxedema are allied manifestations of the same underlying pathologic condition, toxic diffuse goiter. I was unaware of the sparsity of recorded cases demonstrating this association.

A recent review of 13 cases of localized myxedema seen at the Cleveland Clinic showed that all the patients had had thyroidectomy for toxic diffuse goiter prior to the appearance of the localized myxedema. There was a record of an associated exophthalmos in 7 cases. Three patients had severe progressive exophthalmos. With a Cleveland colleague, I recently observed a patient in whom progressive exophthalmos and localized myxedema appeared during the treatment of toxic diffuse goiter with thiouracil. A surgical thyroidectomy had not preceded medical treatment. Thus there are 3 additional unrecorded cases of toxic diffuse goiter in which the progressive exophthalmos and localized myxedema developed concurrently. Exophthalmos has been observed in toxic diffuse goiter more often than has localized myxedema. It is probable that mild cutaneous changes have been overlooked in cases of progressive exophthalmos. Furthermore, histologic sections of pretibial skin from patients with progressive exophtalmos and with absence of clinical localized myxedema might show foci of myxedematous degeneration, which may not become recognizable clinically. Dr. Curtis' hypothesis suggests that this investigation is indicated.

The diagrammatic presentation of the concept of the thyropituitary axis clearly explains some of the perplexing features of localized myxedema, particularly its development in toxic diffuse goiter after the administration of thiouracil or after thyroidectomy. Furthermore, the presentation also explains the failure of localized myxedema to disappear after the administration of thyroxin and thyroid extract.

If the concept of the thyropituitary axis is correct, and since it has not been determined that additional and more complex hormone relationships may be of etiologic importance in toxic diffuse goiter and in progressive exophthalmos and localized myxedema in particular, the logical therapeutic approach should be directed toward decreasing the production of the thyrotropic hormone. Roentgen ray treatment of the pituitary gland has been helpful in some cases of progressive exophthalmos. Dr. Curtis has referred to a patient with severe progressive exophthalmos and localized myxedema, whose case I presented at a meeting of the Cleveland Dermatological Society. In this patient, because of severe exophthalmos, the left orbit was decompressed and the anterior lobe of the pituitary gland was cauterized. After this procedure the localized myxedema disappeared

and the proptosis regressed. Obviously, such a radical procedure is contraindicated in the treatment of localized myxedema. Although recorded cases identical with this are not numerous, the observation in itself lends strong support to Dr. Curtis' hypothesis.

It is unfortunate that there is no simple and safe procedure for inhibition of hyperfunction of endocrine glands other than the thyroid. The mechanism in the production of localized myxedema and the reason for the predilection of the condition for the pretibial areas remain to be determined. Dr. Curtis suggested that the edema-producing quality of the thyroid-stimulating hormone, which probably contributes to the evolution of progressive exophthalmos, likewise initiates localized myxedema. Recently Watson has shown that the skin in pretibial myxedema contains an excess of hyaluronic acid, and he has expressed the opinion that the myxedema is related to disturbance of the hyaluronic acid–hyaluronidase balance. Further investigation may show that hormones influence the action of cutaneous enzymes which are active in the metabolism of mucopolysaccharides present in the interfibrillar substance of collagen tissue.

We are indebted to Dr. Curtis for emphasizing the association of progressive exophthalmos and localized myxedema and for pointing out their parallel clinical course. I concur in his hypothesis that they are allied manifestations of toxic diffuse goiter.

DR. MARTIN F. ENGMAN JR., St. Louis: I should like to ask Dr. Curtis to say something about the factor of heredity.

DR. PAUL A. O'LEARY, Rochester, Minn.: I was intrigued by Dr. Curtis' conception of localized myxedema because of my interest in this condition for many years. In a paper I presented on this subject in 1930, I purposely avoided the use of the term localized myxedema because the late Dr. Henry Plummer objected strenuously to the concept that myxedema and hyperthyroidism in the form of toxic diffuse goiter could occur in the same patient at the same time. Practically all the patients in the early cases we studied who presented plaques of solid edema of the extremities had recently gone through an episode of hyperthyroidism of the toxic diffuse goiter type, and some were experiencing a second episode following a postoperative remission. It was my feeling at that time that this complication was seen most frequently in those persons who had had severe edema of their lower extremities as a result of myocardial disease secondary to the hyperthyroidism.

Since then I have seen several patients with localized plaques of solid edema, with histologic evidence of myxedema, in whom clinical, laboratory and historical evidence was lacking for hyperthyroidism, either past or present. Likewise exophthalmos was not present in all our patients who manifested these plaques.

For this reason the work of Meyer, followed by that of Watson and Pierce, as mentioned by Dr. Netherton, advanced an interesting concept, namely, that mucin was precipitated in the skin and elsewhere as a result of a disturbance in the hyaluronidase balance—possibly the result of an interference in the counter-reaction function of a theoretic enzyme. Although prepared to do so my associates and I have not as yet had the opportunity, because of lack of case material, to apply the suggestions of these investigators.

One other point is that in all the cases we have been able to follow the plaques eventually disappear spontaneously, occasionally in four to five years, even though some of the patients retain evidence of hyperthyroidism.

DR. HERMAN SHARLIT, New York: I too have been interested in this report by Dr. Curtis. It should be taken into consideration in explaining the

background for localized infiltration of mucin that physicians frequently see these conditions locally, particularly in the legs, with no apparent clinical evidence of glandular deficiency. Recently my associates and I treated at least 2 patients with hyaluronidase enzymes, and the reaction was immediate and spectacular. It may be that, in studying this enzyme and the hyaluronic acid reaction, investigators are getting more to fundamentals behind the infiltration of mucin by taking a larger picture. It may be that there is more than one mechanism that results in the production of mucin.

DR. FRED D. WEIDMAN, Philadelphia: I should like to ask Dr. Curtis whether there is evidence that mucinoid degeneration occurs in the involuntary muscles. The skin is the particular field of us present, and I am wondering whether we can pick up early evidence of this dystrophy in a simple histologic examination of the skin. Time and time again I have felt that the muscles appeared far too broad and edematous in proportion to the development of the hair follicle. Would this material in the involuntary muscles be mucin? The mucin in myxedema is a different kind of mucin from that observed in epithelial structures; it has a definite chemical reaction. It will not reduce Fehling's solution without preliminary hydrolysis. Perhaps we may learn something in examination of the skin that will bear no relation to the mucinoid degeneration in the involuntary muscles, whether it is connected with hyperthyroidism or not. I recommend that in future studies of diseases of this kind the condition of the arrectores pilorum be inquired into.

DR. ARTHUR C. CURTIS, Ann Arbor, Mich.: I wish to thank the discussers for their interesting and constructive ideas. Dr. Netherton asked why localized myxedema appeared on the legs. I neither know why nor whether this occurrence has anything to do with dependency of the extremities. I agree with Dr. Netherton that patients who have progressive exophthalmos often have cutaneous lesions which are overlooked. In one of our patients with malignant exophthalmos (case 2), lesions on the shins, which from their description were probably localized myxedema, were present.

The role of the pituitary gland in toxic diffuse goiter was shown by Means,[18] who reported the case of identical twin girls, 1 of whom acquired round worm infection. The passage of these worms was so shocking to the child that she acquired toxic diffuse goiter. That the pituitary gland was involved in the case of this adolescent girl is shown by the fact that after having the disease she grew 1½ inches taller than her twin. Fourteen years ago Plummer and Wilder[17] speculated on the possible association of progressive exophthalmos and localized myxedema and suggested tentatively that they might be due to the same factor and both related to an overfunction of the anterior lobe of the pituitary gland.

Dr. O'Leary used the term solid edema in his excellent article on this subject.[21b] Solid edema is a better term than localized myxedema.

Dr. Sharlit mentioned cases of localized mucinous infiltration without apparent evidence of glandular deficiency. I have not seen such cases, nor have I had any experience with determination of the presence of hyaluronic acid in these diseases, but I think these points provide a fertile field for future endeavor.

Dr. Weidman mentioned the possibility of mucinous degeneration in the arrectores pilorum. In toxic diffuse goiter the smooth muscles do show change, but I have not observed mucinous degeneration in the smooth muscles of the skin because I have not looked for it. I shall investigate this problem further when I return.

PROMIN® IN THE TREATMENT OF CERTAIN DERMATOSES

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THE therapeutic effects of promin® (sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) were studied in a group of common dermatoses. Senior members of the staff of the Department of Dermatology of the University of Pittsburgh School of Medicine participated in the study, and their independent observations were used as a basis for this report.

A total of 81 patients were treated with the drug for periods ranging from two weeks to twenty-seven months. The patients were arbitrarily divided into two groups. The first group consisted of 33 patients (table 1), whose disease was primarily of the chronic type, which had failed to respond to previous therapy. In the second group there were 48 patients (table 2) whose diseases were the more acute forms of dermatoses. Promin® was administered orally against all diseases except scleroderma, against which intravenous therapy was used. The oral administration consisted of a daily dosage of 0.8 to 1.8 Gm. of the drug and was continued over treatment periods of four weeks to twenty-seven months. Intravenous therapy was given daily in dosage of 2.5 to 5 Gm. for two weeks, then 5 Gm. weekly over a period of four months. The oral administration of 1.8 Gm. daily could be continued only for a relatively short period (ten to fourteen days) whereas a smaller dosage of 0.8 to 1.2 Gm. was tolerated longer (two to twenty-seven months). The regimen of treatment was not interrupted unless toxic symptoms appeared.

Promin® jelly (5 per cent of the agent in a tragacanth base) was used as a local application in all instances. Prior to treatment physical examinations of the patients were made, including a blood count and urinalysis. Patients were examined biweekly for the first month, then weekly as long as treatment was continued. Urinalyses and red and

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Dr. E. A. Sharp, director of clinical investigation, Parke, Davis & Company, Detroit, supplied the promin®.

white blood cell counts were performed for each patient every two weeks. The toxic reactions which were encountered are worthy of report. One of the most distressing from the point of view of the patient was a peculiar discoloration of the skin, which appeared within eight to forty-eight hours as a peculiar, dusky, slate gray or bluish tint. It first appeared about the lips, tip of the nose, cheeks, neck, extremities and body in the order named. The intensity varied with the natural pigmentation of the skin and was unmistakable in members of the white race. A detectable change in color was discernible in the Negro patient and was most prominent on the sclera and on the oral mucosa. The discoloration was not associated with any appreciable numerical reduction of the erythrocytes or hemoglobulin, and in no instance was there any evidence of

TABLE 1.—*Results of Promin® Therapy Against Chronic Dermatoses*

Disease	Cases	Improved	Unimproved	Reactions
Chronic discoid lupus erythematosus	14	3	11	14
Chronic disseminated lupus erythematosus	5	2	3	5
Sarcoidosis	3	0	3	3
Erythema induratum	2	0	2	2
Lupus vulgaris	4	0	4	4
Scrofuloderma	2	1	1	2
Scleroderma (diffuse)	3	1	2	3

TABLE 2.—*Results of Promin® Therapy Against Acute Forms of Dermatoses*

Disease	Cases	Improved	Unimproved	Reactions
Erythema multiforme	8	2	6	6
Erythema nodosum	4	1	3	3
Acute infectious eczematoid dermatitis	14	0	14	13
Impetigo contagiosa	8	0	8	8
Ecthyma	4	0	4	3
Sycosis vulgaris	4	0	4	4
Furunculosis	4	0	4	4
Acute disseminated lupus erythematosus	2	0	2 (died)	2

cardiorespiratory embarrassment. This discoloration did not occur in the patients who received intravenous therapy. Headaches, mild and severe, were common, annoying and appeared within forty-eight to seventy-two hours. Nausea, vomiting, vertigo, myalgia, insomnia, urticaria and malaise were encountered. Dyspnea, palpitation, hematuria and albuminuria were absent. A numerical reduction in the number of erythrocytes and hemoglobulin was observed in 9 patients and appeared within six to eight weeks. Leukopenia, peculiar to lupus erythematosus, was not generally affected as a rule. However, in 5 patients a definite elevation of the leukocyte count was maintained by the administration of the drug and was accompanied with definite clinical improvement. Recticulocytosis occurred on three occasions and appeared several days after the observation of a numerical reduction of the erythrocytes. All reactions were controlled by withdrawal of the

drug, and no permanent sequelae were encountered. A routine of discontinuing treatment for one week after three weeks of treatment resulted in fewer and milder reactions and allowed us to continue treatment in 2 instances for periods of eighteen to twenty-seven months without incident. Only 5 patients disclaimed toxic reactions, and these belonged to the second group. The local use of promin® jelly produced contact dermatitis in 2 patients.

REPORT OF CASES

The results from the use of promin® orally, parenterally and locally were not encouraging. Of the 81 patients treated, 10 were improved and 71 were unimproved. The local use of promin® jelly had no specific curvative effect. Four cases warrant mention:

CASE 1.—A woman aged 27 had patches of discoid lupus erythematosus for three years. With promin® therapy complete healing occurred in four weeks, but due to the appearance of a persistent bluish tint of the face, further treatment was refused. A recurrence began within three weeks after withdrawal of the drug.

CASE 2.—A man aged 52 had ulcerative lesions of lupus erythematosus of the lips of five years' duration; these promptly healed within two weeks after the initiation of treatment. Recurrence developed ten days after withdrawal of the drug, which caused nausea and severe headaches. Alternating periods of one week of treatment and one week without treatment resulted in complete healing, which was maintained over a period of six months.

CASE 3.—A man aged 51 had chronic discoid lupus erythematosus of twenty-seven years' duration, which healed within eight weeks and remained healed over a treatment period of twenty-one months on a daily dosage of 1.5 Gm. of promin®.

CASE 4.—A woman aged 32 had a generalized scleroderma of three years' duration, associated with ulcerative sclerodactylia which began four months prior to treatment with the drug. The ulcerative lesions then healed within one month. Treatment was continued during the latter half of a pregnancy, which terminated normally at full time. Discernible changes were not observed in pathologic examination of biopsy specimens taken at intervals of six months.

SUMMARY AND CONCLUSION

The use of promin® (sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate) in the treatment of a group of common dermatoses was disappointing. Toxic reactions were common. Therapy with this drug offers no advantage over the recognized treatment regimens against the group of dermatoses studied.

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CIRCUMCISION AND VENEREAL DISEASE

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THERE has been little written from a statistical standpoint to confirm or deny the popular medical belief that the circumcised are less prone to contract venereal disease. This paper will present a statistical study of the incidence of circumcision in a group free from venereal disease as compared with that of groups with various forms of venereal disease, to determine the influence of circumcision on venereal disease.

The material for this study was obtained during 1945 from the venereal clinics of the United States Naval Hospital at St. Albans, N. Y.

NO VENEREAL DISEASE

From a group of 790 gentiles, 525 Jews and 76 Negroes who had never had venereal disease it was found that 34 per cent of the gentiles, almost all the Jews and 42.2 per cent of the Negroes were circumcised. The 1 uncircumcised Jew was unorthodox and proud of his prepuce. It was difficult to find many Negroes of military age without a venereal history.

VENEREAL DISEASE

Gonorrhea.—Of 522 gentiles, 16 Jews and 544 Negroes who gave a history of gonorrhea, 23.6 per cent of the gentiles, 100 per cent of the Jews and 13 per cent of the Negroes were circumcised. The percentage of circumcised gentiles and Negroes was definitely lower in the group with gonorrhea than in the group that never had had venereal infection. Brietenstein [1] also found this true, as did Lloyd and Lloyd,[2] who found that 27.6 per cent of the gentiles with gonorrhea had been circumcised, an observation almost identical with that in this study.

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Read before the Section on Dermatology and Syphilology at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 12, 1947.

1. Brietenstein, cited by Bloch, I.: The Sexual Life of Our Time, in Its Relation to Modern Civilization, translated from the 6th German edition by M. E. Paul, London, Rebman, Ltd., 1908, p. 376.

2. Lloyd, V. E., and Lloyd, N. L.: Brit. M. J. 1:144, 1934.

The scarcity of Jews with gonorrhea in this study was striking. Berkowitsch [3] found the gonorrhea rate the same in Jews and in gentiles. Physicians at this hospital who had worked in the venereal clinics of New York city informed me that gonorrhea was common in Jews but more prevalent in gentiles. It is likely that some Jews went to their private physicians for treatment of gonorrhea, particularly at the time when venereal disease carried with it the penalty of misconduct with loss of pay.

Syphilis.—In 1855 Jonathan Hutchinson [4] first made the observation that syphilis was uncommon in Jews. This was confirmed by Feldman [5] in a study at the venereal clinics of Metropolitan Hospital in 1882, where syphilis was found to be four times more common in gentiles. Polduan,[6] in a study of the vital statistics of New York city, found syphilis to be three times more prevalent in gentiles. Circumcision, being almost universal in Jews, was considered to be the reason for this situation. Brietenstein,[1] in a study of 15,000 circumcised African soldiers and 18,000 European soldiers, many of whom were uncircumcised, found venereal disease, including syphilis, to be commoner in the uncircumcised. Lloyd and Lloyd,[2] at Guy's Hospital, concluded that circumcision was not an important factor in acquisition of syphilis, but they did not compare their percentages of circumcised and uncircumcised with those observed in groups that had no history of venereal disease.

The 532 cases of syphilis in this series were in 344 gentiles, 4 Jews and 184 Negroes; of these, 22.2 per cent of the gentiles, 17.5 per cent of the Negroes and all the Jews were circumcised. The paucity of Jews in this group could be due to the same reason as that suggested in the discussion of the group with gonorrhea. Syphilis certainly was less common in circumcised gentiles and Negroes. This observation becomes even more striking when these cases are subdivided into the following groups: 358 cases with primary syphilis on the distal end of the penis, where the presence or absence of the prepuce could affect the acquisition of syphilis; 88 cases with the primary sore on the middle or upper portion of the shaft or some other part of the body with secondary lesions, and 86 cases with no history of primary or secondary sores.

3. Berkowitsch, M. E.: Ostasiat. Rundschau **3**:19, 1928.

4. Hutchinson, J.: M. Times & Gaz. **11**:542, 1855.

5. Feldman, W. M.: The Jewish Child, New York, Bloch Publishing Company, 1918, p. 213.

6. Polduan, C., and Weiner, L.: New England J. Med. **208**:407, 1933.

The 358 persons with primary syphilis on the distal end of the penis included 216 gentiles and 142 Negroes; of these 13.9 per cent of the gentiles and 12.7 per cent of the Negroes were circumcised.

The 88 with primary syphilis not on the distal end or with secondary lesions included 72 gentiles, 2 Jews and 14 Negroes; 47.3 per cent of the gentiles, 29 per cent of the Negroes and all the Jews were circumcised at the time of their infection. Though there is a slight difference between the figures given for this subgroup and those for persons without venereal infection, attention is called to the decidedly increased percentage of circumcised in it when compared with the aforementioned group of the persons with primary sores on the distal end of the penis.

The 86 who gave no history of primary or secondary lesions consisted of 56 gentiles, 2 Jews, and 28 Negroes; 21.4 per cent of the gentiles, 35.7 per cent of the Negroes and all the Jews were circumcised. Here again the percentage of circumcised is higher than in the group with primary lesions on the distal end of the penis. In both groups of those without primary sores on the distal end, 36 per cent of the gentiles and 33 per cent of the Negroes were circumcised, a figure which is almost identical with that given for the group free from venereal disease.

The diagnosis of syphilis was usually made earlier and with less difficulty, with a better clinical result, in the circumcised. This situation existed because many of the uncircumcised were phimotic from birth or had inflammatory phimosis develop as a result of the induration and edema associated with the chancre, this development making the retraction of the foreskin impossible, a result which made the dark field examination difficult. The presence of Vincent's organisms under the phimosis also confused the diagnosis. The primary sores were usually single in the circumcised and multiple in the uncircumcised.

Ulcus mixté, or chancroid infection combined with chancre, was much commoner in the uncircumcised. Generally the chancres healed more quickly in the circumcised.

CHANCROID

Chancroid.—Berkowitsch found chancroid six times more frequent in gentiles than in Jews. Lloyd and Lloyd [2] found that 90 per cent of the patients in their series were uncircumcised. In the days prior to the use of sulfonamide drugs, when chancroid infection, particularly the type with buboes, required long hospitalization, Rauschkolb [7] util-

7. Rauschkolb, J. E.: Circumcision in Treatment of Chancroidal Lesions of Male Genitalia: Further Observations, Arch. Dermat. & Syph. **39**:319 (Feb.) 1939.

ized circumcision during the acute stage, with excellent results, shortening the hospital stay. Patients in his series averaged thirty-two days of hospitalization, as compared with the months needed for persons treated with the usual methods advocated at that time.

A diagnosis of chancroid was made in the present series in 138 cases, of which 60 were in gentiles and 78 in Negroes; 91.6 per cent of the gentiles and 96.1 per cent of the Negroes were uncircumcised.

The chancroid lesions were usually multiple in the uncircumcised persons and in the few circumcised patients were single and cleaner. The circumcised persons had quicker healing when treated with sulfonamide compounds than did the uncircumcised. The differentiation from chancre and Vincent's balanitis was difficult in the uncircumcised.

Lymphogranuloma Venereum.—The diagnosis of lymphogranuloma venereum was made for 44 patients, of whom 26 were gentiles and 18 Negroes. All these persons were uncircumcised.

Granuloma Inguinale.—One case of granuloma inguinale was seen in an uncircumcised white person.

The Percentages of Circumcised Persons Among Subjects Without Venereal Disease and Among Those with Various Venereal Diseases

Diagnosis	Jews	Gentiles	Negroes
No venereal disease	99.8%	34 %	42.2%
Gonorrhea	100 %	23.6%	13 %
Syphilis	100 %	22.2%	17.5%
Chancre on distal end of penis	No case	13.9%	12.7%
Chancroid	No case	8.4%	3.9%
Lymphogranuloma venereum	No case	0 %	0 %

NONVENEREAL INFECTIONS

The following interesting observations were made in cases of nonvenereal disease of the penis. The diagnosis of Vincent's balanitis was made for 22 patients, all of whom were uncircumcised and 8 of whom had pronounced phimosis. Vincent's balanitis often recurs. Circumcision is the treatment of choice in that event.

Verruca acuminata of the penis was seen in 61 persons, of whom 40 were gentiles and 21, Negroes. All but 2 of these were uncircumcised. One case of perianal verruca acuminata was seen in a Jew. Verruca acuminata is uncommon in the circumcised, and prior to therapy with resin of podophyllum the treatment of choice was circumcision. Circumcision still is valuable in recurrent cases.

Nonspecific balanitis was not seen in the circumcised.

Herpes progenitalis was seen in this study in about the same proportion in circumcised and uncircumcised patients with venereal dis-

ease as in the group without venereal disease. This observation should mitigate against the popular treatment of this troublesome condition by circumcision.

COMMENT

Venereal infection is less likely in the circumcised because of the physical and histologic changes that occur on the distal end of the penis after circumcision. The skin of the glans, corona, frenulum and inner portion of the prepuce in the uncircumcised is more like mucous membrane, being soft, moist and easily traumatized during love play and coitus, with resulting microscopic and macroscopic tears. The skin of the corona, glans, frenulum and distal portion of the shaft in the circumcised is tough, keratinized, dry and a degree or more cooler than is the area under the prepuce of the uncircumcised. The prepuce, especially when it is phimotic, acts as a sheath holding bacteria acquired during coitus in an excellent moist, warm culture medium, making infection likely through the tears mentioned. The opposite is true of the dry, cool, tough skin of the circumcised.

Another less important reason for circumcised persons' being less prone to acquire venereal disease is that circumcision is usually commoner in those from better educational, financial and cultural backgrounds. This situation gives these persons at least a better chance of proper education regarding sex. Their chances of meeting, associating with and cohabiting, in or out of the marital status, with those women least likely to be infected are somewhat better than are those of the uncircumcised. Proper sex education would give them at least knowledge of the existence of venereal disease and of how it is contracted. It also would provide them with some knowledge of the signs and symptoms, so that, if infected, they seek medical advice early and thus are less likely to infect others of their class.

Through the ages, Jews have universally been circumcised on the eighth day after birth. This procedure has given them protection against venereal disease even when they have been exposed. Though they may be promiscuous in their own race, Jews certainly are less promiscuous than Negroes. When infected they tend to seek medical advice early. Thus venereal disease has not been introduced into the Jewish race generation after generation. Instead the rate has remained the same or decreased, so that the chance of Jews' being infected has decreased.

Circumcision is not common among Negroes. When done it often is later in life and frequently is due to recurrent venereal disease. The sex education of most Negroes is meager. They tend to accept venereal disease with less fear or social taboo than do most Jews and

gentiles. Many Negroes are promiscuous. In Negroes there is little circumcision, little knowledge or fear of venereal disease and promiscuity in almost a hornet's nest of infection. Thus the venereal rate in Negroes has remained high.

Between these two extremes there is the gentile, with a venereal disease rate higher than that of Jews but much lower than that of Negroes.

CONCLUSIONS

Gonorrhea and syphilis are less common in the circumcised.

Chancroid is rare in the circumcised.

Lymphogranuloma venereum is almost never seen in the circumcised.

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MANUAL EPILATION IN TREATMENT OF TINEA CAPITIS

JOHN F. WILSON, M.D.
PHILADELPHIA

SINCE manual epilation has played such an important role in the treatment of tinea capitis throughout the ages, and is still recommended by most authorities as an adjunct to the newer drug therapies and fungicides, and even as an indispensable adjunct to curative roentgen epilation, a more precise evaluation of its exact therapeutic significance might lead to progress in the management of tinea capitis, most particularly in the control of epidemics of this disease.

A study, therefore, was made of the results of treatment in three groups of cases; in one, serving as the control group, local application of a fungicidal ointment was the only therapy used, and in two this local therapy was supplemented by manual epilation of shorter and longer duration. The results obtained will be described in detail, as a preliminary step toward the demonstration of the actual part played by manual epilation, per se or in combined treatments, for the cure of tinea capitis.

As early as the third century B.C., Heliodorus [1] recommended the application of a skull cap made of pitch plaster for removal of hairs in tinea capitis, the true cause of which was, of course, unknown at that time. The warmed pitch was spread on linen and applied to the scalp, and, after being permitted to cool and harden, this cap was removed by a sudden wrench, carrying the hairs with it. Although this method was later abandoned as being too barbarous, Sabouraud [1] stated that, properly applied, it was far from being as painful as described, and that he found this method in use in some French provinces as late as the beginning of the twentieth century. After the substitution of less painful, but apparently likewise less efficient, methods, physicians of that period reported a higher incidence of the disease in hospitals, where its spread was particularly difficult to control, and where the pitch cap had proved of real help.

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Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 23, 1948.

1. Sabouraud, R.: Du role de l'épilation a la pince en dermatologie, Presse méd. **39**:113-115, 1931.

Manual epilation, or epilation with the aid of forceps, was probably first used by the Arabs, who constructed the finest brass instruments for this purpose, comparing favorably with the most modern epilation forceps. Bazin [1] and his followers revived epilation as a method of treatment for tinea capitis. Besnier devoted one morning weekly to the clinical study and teaching of this form of therapy. Its steady application for about a century resulted in perfection of technic and the development of many experts in the art of epilation. As enthusiasm for this procedure once again waned, it was kept up chiefly by individual advocates, each with his own favorite technic. Thus, Hebra [2] proceeded by "holding the hairs indiscriminately and in thin tufts between a blunt edged instrument, a tongue spatula, for instance, and the opposed thumb, and then drawing them out. With slight traction the diseased hairs come out, the healthy ones remaining in the follicles." When manual epilation once again returned to favor, it was chiefly accomplished with forceps, but the dosage and duration of such treatment remained completely arbitrary.

During the many centuries that have elapsed since manual epilation came into vogue, almost innumerable methods of treatment for tinea capitis have been suggested, tested and abandoned. It is remarkable that epilation, though occasionally relegated to the background or temporarily abandoned, has always been restored to favor, and, finally, with the discovery of roentgenotherapy as a means of epilation has become the treatment par excellence for tinea capitis. Moreover, cure by roentgen epilation cannot be assured without the adjunct of manual epilation.

This fact and the possibility that some of the therapeutic results claimed for the newer fungicides and other agents may be attributable to the manual epilation described as an adjunct, rather than to the various local applications per se, have been mentioned by various writers.[3] As previously emphasized, the dosage and duration of manual epilation prescribed have varied with the individual author. Some physicians instruct their patients to pull out infected hairs daily.[3c] Some epilate twice weekly in the office.[3e]

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2. Hebra, F.: On Diseases of the Skin, translated by C. H. Fagge, London, 1866-1868.

3. (*a*) Hartzell, M. B.: Diseases of the Skin, ed. 1, Philadelphia, J. B. Lippincott Company, 1917. (*b*) Steves, R. J., and Lynch, F. W.: Ringworm of the Scalp, J. A. M. A. **133**:306-309 (Feb. 1) 1947. (*c*) Miller, J. L.; Lowenfish, F. P., and Beattie, G. F.: Local Treatment of Tinea Capitis, ibid. **132**:67-70 (Sept. 14) 1946. (*d*) Schwartz, L.: Progress in Fungous Disease Therapy, Journal-Lancet **67**:56-59 (Feb.) 1947. (*e*) Peck, S. M.: Suggested Methods for the Control of the Present Epidemic of Tinea of the Scalp, Pennsylvania M. J. **50**:569-573 (March) 1947. (*f*) Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 2, Chicago, The Year Book Publishers, Inc., 1943.

Roentgen irradiation, while the most effective form of therapy, is of value only in experienced hands, and an adequate number of experienced roentgenotherapeutists may not be available, particularly in time of epidemics.[3b] Thallium acetate is indicated only in selected cases and is, besides, extremely toxic. It has been suggested and experiments have shown that the fatty acids secreted by adult hair may play some part in rendering adults immune to infection by tinea capitis.[4] These therapeutic measures are, however, still in the experimental stage. The discovery of an agent that would increase the penetration of fungicides might render even manual epilation superfluous.

There are, too, cases in which tinea capitis persists in spite of the most arduous manual epilation. It has been observed that a few hairs may continue to fluoresce under the Wood light for weeks or months after the rest of the affected area has cleared. Hairs may cease to fluoresce temporarily, only to show up at a later examination. Among the factors believed to play a part in this stubborn chronicity of the disease have been mentioned the presence of infected loose scales; the removal of healthy hairs, so that the follicles are left open for invasion by the organisms, and, finally, the breaking off of diseased hair with a portion of the infected hair left in the follicle to infect the new hair as it forces its way to the surface.

The present study is not intended as a brief for manual epilation as a curative treatment for tinea capitis. As a matter of fact, it has been truly stated that any treatment of this disease is still in the experimental stage.

Spontaneous cure of tinea capitis occurs at the age of puberty and in younger children in from 10[3f] to 27[5] per cent of cases. For this reason the real contribution of any therapeutic measure will be exceedingly difficult to assess.

One of the chief stumbling blocks in the application of manual epilation as a treatment for tinea capitis in the past was the degree of training and experience required to distinguish infected hairs from normal hairs, thus enabling one to select the proper areas for epilation. Some claimed that the diseased hairs could be recognized by a reddening about the follicular orifice; others applied chloroform to the scalp, claiming that with it infected hairs assumed a whitish appearance. This difficulty was overcome, in 1903, when the Wood filter lamp was introduced. Under ultraviolet light the diseased hairs become fluorescent and can be easily distinguished from normal hairs. Manual

4. Rothman, S.; Smiljanic, A.; Shapiro, A. L., and Weitkamp, A. W.: Spontaneous Cure of Tinea Capitis in Puberty, J. Invest. Dermat. **8**:81-98 (Feb.) 1947.

5. Livingood, C. S., and Pillsbury, D. M.: Ringworm of the Scalp, J. Invest. Dermat. **4**:43 (Feb.) 1941.

epilation can be accomplished accurately and thoroughly with this aid. The filter, which is composed of glass with barium silicate and nickel oxide components, permits transmission of only certain wavelengths, and under this light the diseased hairs take on a bright, pale green color, described variously as luminous yellowish green or bright bluish green.

The present study includes the results of observation of 104 cases of tinea capitis due to the Microsporum audouini.[6] Cases of tinea due to other organisms were excluded, since such infections are usually associated with inflammation, which aids spontaneous cure and therefore complicates the interpretation of results. Moreover, it is M. audouini which is responsible for the most chronic and epidemic forms of the disease. In 16 of these 104 cases, as a reaction some form of kerion developed during treatment, and they were therefore excluded from the series, leaving 88 cases for the study. Because of the need for long-continued study of the patients, it was decided to give them all some form of local treatment, in order to insure a more successful period of observation. This local treatment consisted in application of an ointment[7] containing 5 per cent undecylenic acid, 3 per cent triethanolamine U. S. P., 20 per cent zinc undecylenate, 3 per cent sodium tetradecyl sulfate (sodium-2-methyl-7-ethylundecyl sulfate-4), 10 per cent propylene glycol N. F. (racemic 1-2-dihydroxy-propane), 10 per cent propyl alcohol and 49 per cent carbowax 1500® (a mixture of polyethylene glycols having an average molecular weight of about 550).

The cases were divided into three groups; in the first, which served as the control group, no manual epilation was carried out and only the ointment was used. In the second group, manual epilation of the scalp hairs was carried out for approximately one minute, every two weeks. In the third group, manual epilation was carried out for five minutes, every two weeks. I performed all the epilation.

TECHNIC

The following routine was carried out on all patients:

1. The heads were shaved once weekly, the morning after examination.
2. The heads were shampooed with castile soap once weekly.
3. The ointment was rubbed into the affected areas three times a day for five minutes at a time.
4. A tight-fitting cap with a paper lining was worn by the patient; this lining was changed once daily and the discarded one burned.
5. The patients were asked to return every two weeks for follow-up examination, at which time they were all examined under the Wood filter light.

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6. Forty-eight cultures were made by Dr. Dorothy Spring, Department of Health Laboratories, Pennsylvania Department of Health.
7. This ointment was supplied by Wallace & Tiernan Products, Inc., Belleville, N. J.

Special attention was given to the epilation of the mother patch or patches, the name given to the area or areas of greatest involvement in the infection. When epilation was concentrated in this area, many of the scattered infected hairs in other areas were spontaneously cured. In addition, it was noted that if manual epilation was not stressed in these areas progress was slow.

Hairs were removed with plain cilia forceps.

A follow-up examination with the Wood filter after four months was used as a criterion of cure.

RESULTS

Of the 39 patients in the first, or control, group treated exclusively with ointment, 11, or 22.8 per cent, were cured. Of the 17 patients in the second group, given one minute epilation every two weeks in addition to the ointment treatment, 6, or 35.2 per cent, were cured. Of the 32 patients in the third group, given manual epilation for five minutes every two weeks, in addition to the ointment treatment, 18, or 56.2 per cent, were cured.

In the control group, the time required for cure in 9 cases varied from 98 to 293 days, the average being 193.4 days. In group 2, the time required for cure in 6 cases varied from 72 to 243 days, the average being 171.5 days. In group 3, the time necessary for cure in 18 cases varied from 46 to 384 days, with an average of 185.5 days.

In view of the variation in the individual patient's response to treatment, together with the wide variations in extent of involvement of infections with this disease, it is difficult to correlate the time necessary for cure in each group with the total time spent in manual epilation in that group. However, group 3 included a large number of patients with extensive involvement of the scalp, and previous to this study many of them had been subjected to various types of treatment.

Regardless of the length of time treated, the patients for whom manual epilation was used improved continuously under treatment. Only patients with very extensive infection failed to respond, and even in such patients, if the treatment is continued for a sufficient period, the infection can be eradicated.

SUMMARY

Three groups of patients with tinea capitis were treated.

In the control group, who had no manual epilation, 22.8 per cent of the patients were cured. Of the patients who were given epilation for about one minute every two weeks, 35.2 per cent were cured. Of the patients who were given epilation for five minutes every two weeks, 56.2 per cent were cured.

It is concluded that manual epilation is definitely of value in the treatment of tinea capitis, regardless of other methods used.

2013 Delancey Street.

ABSTRACT OF DISCUSSION

DR. W. A. SHOWMAN, Tulsa, Okla.: Manual epilation in treatment of tinea capitis due to M. audouini has received considerable attention in the past few years and Dr. Wilson has furnished additional evidence that this infection can be treated successfully by this method. It is interesting to note from his report that the total number of cures in those cases in which epilation was carried out in addition to topical application was much higher; yet the extension of the time factor in the epilating process did not shorten the total number of days that was required to obtain a cure. It is obvious that the total number of infected hairs removed per unit of time depends a great deal on the operator, and the longer the duration of the epilation procedure, the shorter the total treatment period should be, a supposition which is not substantiated by the report, since it required an average of 185.5 days for group 3 and an average of 171.5 days for group 2. Complete epilation is the most important factor.

I agree with the author that forced regulation for the care of infected patients is imperative, but any stipulated time factor for the epilation is not essential, provided that a careful and thorough epilation be performed. Pillsbury (Scully J. P.; Livingood, C. S., and Pillsbury, D. M.: The Local Treatment of Tinea Capitis Due to M. audouini, *J. Invest. Dermat.* **10**:111 [March] 1948) stated that 90 per cent of cures may be expected with compulsory and supervised treatment. They insisted that careful epilation of all fluorescent hairs be performed in conjunction with topical application. Since the introduction of the purple X® Bulb (Dennie, C. C., and Morgan, D.: Use of the Purple X bulb in Diagnosis of Fungous Diseases of the Scalp, ARCH. DERMAT. & SYPH. **55**:396 [March] 1947), a more careful manual epilation can be done in the home.

Fortunately, those of us practicing in Oklahoma have not had to contend with an epidemic of tinea capitis due to M. audouini during the past five years, as revealed by a questionnaire from seven dermatologists reporting from the state. A total of 550 cases of all types of tinea capitis were reported from private practice for the past five years. From the physicians reporting who furnished culture identification of the causative organism, an incidence of 4.8 per cent due to M. audouini was obtained. Six of the seven reporting dermatologists resorted exclusively to manual epilation in conjunction with topical treatment. One physician reported that in 15 cases epilation by irradiation was used.

I am in accord with Dr. Wilson that manual epilation in conjunction with topical treatment will effect cure in a high percentage of cases of tinea capitis, though infection with M. audouini has not been a major problem in my area.

DR. LOUIS SCHWARTZ, Bethesda, Md.: I agree with Dr. Wilson that manual epilation shortens the time required to cure tinea capitis. Manual epilation removes infected hairs and enables the fungicide applied to the scalp to penetrate the empty infected follicles more easily and kill the fungi lodged there. It has certain advantages over roentgen epilation. Only infected hairs are removed and disposed of immediately. There is no danger of permanent alopecia, and no expert technic is required.

The method of treatment used by Dr. Wilson was similar to that used by the United States Public Health Service at Hagerstown, Md.; Elkhardt, Ind., and several smaller places where there were epidemics of tinea capitis and where from 90 to 100 per cent of cures were obtained among a total of about 1,500 cases.

The important differences between Dr. Wilson's method and the method used by the Public Health Service are that with the latter epilation of the children in the schools was performed daily under a Wood light and that trained attendants

administered the treatment. Moreover, of seventeen fungicides tried by the Public Health Service, the most efficacious was selected; the one used by Dr. Wilson ranked seventh among these. These differences are sufficient to account for the increased percentage of cures and the shorter time required for a cure reported by the Public Health Service. The fungicide which proved most efficacious was a mixture of 5 per cent salicylanilid® (a compound formed by heating a mixture of salycylic acid, aniline and phosphorus trichloride), a powerful industrial fungicide, and 1 per cent hyamine (a quaternary ammonium compound) 1622, a fungicide and cationic detergent, in carbowax 1500® (a mixture of polyethylene glycols), a water-soluble waxy substance with penetrant properties.

Almost as efficient was a mixture of 5 per cent copper undecylenate in carbowax 1500,® or 5 per cent copper undecylenate in carbon tetrachloride, a powerful solvent, with fungicidal properties, which helps to carry the fungicide into the follicles.

The treatment consisted in placing the child under a Wood light every school day and pulling out with forceps the fluorescent hairs in small isolated patches and in epilating conspicuously loose fluorescent hairs in the larger infected areas, before rubbing in the fungicide. The hair was clipped with electric clippers every ten days.

DR. T. BENEDEK, Chicago: I think it was worth while to recall the usefulness of a technic which up to fifty years ago, though painful and tedious, had been the only method of treatment of tinea capitis of the scalp. This technic is not the method of choice; yet it has retained its usefulness in certain instances, as in removal of a few scattered infected hairs on the scalp or, in the case of roentgen epilation, of a few hairs at the curved edges of the hair line not reached by the radiation. There is even an absolute indication for manual epilation when the eyebrows and/or eyelashes are infected concurrently with a microsporum infection of the scalp. I had 3 cases of this kind; in 2 the eyebrows were infected and in the third numerous eyelash hairs of the upper lid of one eye were infected. These hairs were epilated manually under Wood light, and the regrown hairs were normal.

I should like to ask Dr. Wilson whether he carried out cultural investigations in connection with the application of undecylenic ointment. If so, I would like to know the result of such studies during the four month follow-up period. It would be interesting to know the shortest period within which the hairs treated with undecylenic ointment did not show any cultural response and the longest period within which the hairs so treated still yielded a culture of the organisms.

I carried out similar investigations with salicylanilid® ointment, introduced by Schwartz and his associates. In 40 consecutive cases of M. audouini infection of the scalp, hairs were epilated under Wood light every two weeks, for cultural control. Fifteen to eighteen hairs from different foci were distributed in three glucose agar slants. Each hair yielded a normal colony of M. audouini, without the slightest retardation of growth, as compared with untreated hairs infected with M. audouini used as controls. For periods up to 112 days these hairs infected with M. audouini which were treated with salicylanilid® yielded normal colonies, without even the slightest retardation of growth, which at least was anticipated. Salicylanilid® caused severe irritation in the form of suppurative folliculitis when applied after roentgen irradiation. This reaction, however, was seen, peculiarly, only in areas of infected hairs.

In this group of cases were three families, in two of which one sibling, and in the third two siblings, were infected during the treatment with salicylanilid® of the first affected sibling. All these observations reveal, obviously, that there is at present still one method of choice for the treatment of tinea capitis, that is, the Kienböck-Adamson five point method of total epilation.

DR. H. V. ALLINGTON, Oakland, Calif.: My associates and I agree with Dr. Wilson's recommendation of manual epilation and local medication in the treatment of tinea capitis. We have in our laboratory a technician trained to teach the parents the technic of manual epilation. She demonstrates to them the fluorescence of the hairs and the localization of the areas of involvement on the scalp in natural illumination and under the Wood light and, finally, under the purple X® globe. We do not insist that the parents purchase a purple X® globe but we recommend it.

The actual demonstration in the office with the purple X® globe proves, first of all, that the hairs in the case at hand will fluoresce with this source of light; second, it shows the parents what they should see. It has been said that the purple X® globe causes satisfactory fluorescence in only about 50 per cent of cases. However, in our office, the purple X® globe is satisfactory in a somewhat higher percentage of cases.

There are lights available which are designed primarily to show fluorescence in minerals. One of these is on display here at the convention. These are not generally to be recommended for showing fluorescence in infected hairs; they apparently have a wavelength which is not suitable for this purpose.

We instruct the parents to spend whatever time they can each day at home plucking infected hairs. If the patient and his parents are cooperative, it is usually possible to achieve a cure in a large percentage of cases within a relatively short time. If, however, the patient is uncooperative and the parents are timid and ineffectual, it is usually evident within a short time that treatment with manual epilation and local medication will be a tedious process. The method of attack can then be shifted and roentgen epilation resorted to.

DR. WILILAM L. DOBES, Atlanta, Ga.: During the past two years, in Atlanta, there has been an epidemic of tinea capitis due to M. audouini. It was impractical to use roentgen epilation on all clinic patients, and too many private patients refused this procedure because of fear of after-effects. It was necessary, therefore, to resort to local treatment. The newer fungicides, especially salicylanilid,® were found effective in about 60 per cent of the cases, but the treatment persisted for many months. When manual epilation was added, the improvement was more rapid and the percentage of cures higher, but the procedure in most cases was painful to and trying for the patient, as well as for the parent. Many refused this treatment.

The majority of microsporum infections tend to disappear spontaneously at about the time of puberty. Hormonal factors were most likely involved. The use of estrogenic substance was tried by various investigators, such as Lewis and Hopper, Poth and Kaliski, Yanez and others. The results reported varied. I have tried the hormone treatment in more than 50 cases of infection with M. audouini. I doubt whether any patient was actually cured, but I did find that in using a larger dose of estrogens the hair in about 70 per cent of the cases was sufficiently loosened to permit manual epilation without discomfort to the patient. In cases in which local treatment and manual epilation are desired, as an adjuvant treatment I use estrogenic substance, which I give to both men and women. The use of testosterone with men was found satisfactory in only a small number of cases. Results from diethylstilbestrol U. S. P. were not as satisfactory as the estrogenic substance given by injection. Soreness of the breasts was a commoner symptom when diethylstilbestrol was used. The usual dose of estrogenic substance was 10,000 to 15,000 international units every five to seven days. The hair usually

became loose after the third injection. If proper attention was given by the parent, rarely more than six injections were necessary. No ill effects were seen in the patients treated.

DR. LOREN W. SHAFFER, Detroit: I, too, believe in the value of epilation in the management of tinea capitis. However, another factor, spontaneous cure, has not had sufficient emphasis; it should be taken into consideration in evaluating the effectiveness of any prolonged method of treatment. A control group without treatment should be observed.

We physicians in Detroit have had a rather unusual opportunity for studying the rate of spontaneous cure. In 1945 Dr. Lee Carrick made a spot survey on the incidence of tinea capitis in school children of Detroit. On the basis of this survey, it was estimated that there were about 7,000 cases. The management of these cases would have swamped our facilities. No organized program for treatment was developed.

This spring an attempt was made to find and examine the persons who had infections three years ago, in order to learn what has happened to them. We found that a diagnosis of tinea capitis had been made in 1945 in 129 cases and that in all instances the infecting organism was M. audouini. We were much surprised to find that in 70 per cent of these cases the disease had gone on to what we assume to have been largely a spontaneous cure. A few patients may have had fairly adequate treatment, but the great majority had had inadequate or no treatment. Surprisingly, the rate of spontaneous cure was as high among the younger age group as among those near or at puberty.

It is our impression now that the epidemic that was present in our city schools has been subsiding spontaneously, with very inadequate management from a medical and public health standpoint. A survey is to be made again this fall to evaluate this impression.

DR. J. WALTER WILSON, Los Angeles: I want to repeat the warning I voiced at last year's Session regarding dangerous types of ultraviolet radiation for fluorescence examinations. Cold quartz ultraviolet light burners produce 90 per cent of their energy at the level of 2,537 angstrom units. This wavelength produces fluorescence beautifully in hairs infected with tinea capitis due to a microsporum, but it must not be forgotten that it is also capable of producing damage to the patient's eyes and scalp, as well as the backs of the operator's hands.

It is possible to obtain a filter which changes 2,537 angstrom units to 3,650 angstrom units by means of a secondary phosphor, but the production of such a filter is apparently more expensive than many manufacturing concerns care to undertake. Such a filter, however, would eliminate this danger, and one should insist on its being made available if a cold quartz source is to be used.

DR. JOHN F. WILSON, Philadelphia: Spontaneous cure was considered in the study, but the presence of a control group and the method in which the study was carried out should answer Dr. Loren Shaffer's question.

I would like to remind the Section that this paper is not presented in the form of a therapeutic approach to tinea capitis, but is offered simply as an attempt to standardize a long-accepted and valuable treatment of tinea capitis.

DISSEMINATE LUPUS ERYTHEMATOSUS

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DISSEMINATE lupus erythematosus is to be regarded as a systemic disease which in its acute form usually terminates fatally. Cutaneous manifestations do not always predominate; they may be transitory and even in a few cases absent throughout the course of the disease, in which instances one speaks of "lupus erythematosus without cutaneous lesions."

The purpose of this paper is to review the cases of disseminate lupus erythematosus seen at the Mayo Clinic up to 1948. An analysis of 154 cases of disseminate lupus erythematosus up to 1938, together with a review of the literature, was given in "Oxford Medicine.[1]" This survey included a compilation of various studies and papers over a period of years by Goeckerman, Keith and Rowntree, O'Leary, Brunsting and one of us (H. M.). A subsequent report was made in a symposium on lupus erythematosus by Kierland, Montgomery, Stickney, Keith, Slocumb and O'Leary.[2] An analysis of 132 cases of disseminate lupus erythematosus seen at the clinic from 1938 through 1947 is presented here. This includes studies of the so-called lupus erythematosus cell seen in the bone marrow, as described by Hargraves and his associates.[3]

Analysis of various findings in disseminate lupus erythematosus has obviously called for the cooperation of many of our associates in various departments of the clinic. It is impossible to touch on all phases

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Dr. Montgomery is in the Section on Dermatology and Syphilology, Mayo Clinic.

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

1. Montgomery, H.: Disseminate Lupus Erythematosus as a Systemic Disease, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1939, vol. 4, pt. 1, chap. 1-C, pp. 44 (41)-44 (65).

2. Kierland, R. R.; Montgomery, H.; Stickney, J. M.; Keith, N. M.; Slocumb, C. H., and O'Leary, P. A.: Symposium on Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **15**:675-688 (Oct. 23) 1940.

3. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of Two Bone Marrow Elements: The "Tart" Cell and the "L.E." Cell, Proc. Staff Meet., Mayo Clin. **23**:25-28 (Jan. 21) 1948.

because there are various aspects of the subject that call for more intensive study by various internists, as well as by pathologists and other laboratory workers. Thus, for example, the number of cases that should be classified with the Libman-Sacks syndrome with special reference to nonbacterial rather than bacterial verrucous endocarditis, or the number of cases that should be classified as true nephritis rather than simple renal irritation, or a detailed analysis of postmortem findings, necropsy having been performed in 32 of the cases, will not be given in detail.

The concept of lupus erythematosus as a collagenous disease, which view has been championed by the Mount Sinai group, is summarized in recent papers by Baehr and Pollack,[4] by Klemperer [5] and

TABLE 1.—*Analysis of One Hundred and Fifty-Four Cases of Disseminate Lupus Erythematosus (up to 1938)*

Data	Type of Disseminate Lupus Erythematosus		
	Chronic (80 Cases)	Subacute (44 Cases)	Acute (30 Cases)
Women, per cent	61	80	77
Onset as discoid type, per cent	60	34	33
Average age at onset, years	32	30	21
Average age at onset of dissemination, years	39	38	28
Lesions of mucous membranes, per cent	18	23	43
Prodromal symptoms, per cent	5	27	33
Sensitivity to light, per cent	22	23	23
Arthralgia or arthritis, per cent	20	57	63
Fever, per cent	5	57	97
Anemia (less than 4,000,000 erythrocytes per cubic millimeter of blood or a concentration of hemoglobin of 70 per cent or less), per cent	20	52	84
Leukopenia (less than 4,500 leukocytes per cubic millimeter), per cent	22	43	71
False-positive flocculation or Wassermann reaction, per cent	6	11	17
Renal irritation, nephrosis or nephritis, per cent	3	18	32
Infected tonsils, per cent	68	54	40
Deaths attributable to the disease, per cent	8	47	100

in as yet unpublished studies by Baehr and Jarcho ("Oxford Medicine"). The literature regarding disseminate lupus erythematosus has become voluminous. In a five year period, Hench and his associates [6] found fifty-two references to disseminate lupus erythematosus which pertained to associated arthralgias or etiologic concepts regarding the disease, or both. References to significant articles are given in the bibliographies

4. Baehr, G., and Pollack, A. D.: Disseminated Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **134**:1169-1173 (Aug. 2) 1947.

5. Klemperer, P.: The Pathogenesis of Lupus Erythematosus and Allied Conditions, Ann. Int. Med. **28**:1-11 (Jan.) 1948.

6. Hench, P. S.; Bauer, W.; Boland, E. W.; Crain, D. C.; Freyberg, R. H.; Graham, W.; Holbrook, W. P.; Lockie, L. M.; McEwen, C.; Rosenberg, E. F., and Stecher, R. M.: Rheumatism and Arthritis: II. Review of American and English Literature of Recent Years (Ninth Rheumatism Review), Ann. Int. Med. **28**:309-451 (Feb.) 1948.

of the various papers just mentioned and are also made in the seventh edition of Ormsby and Montgomery's text [7] and will not be taken up further in this paper.

TABLE 2.—*Analysis of One Hundred and Thirty-Two Cases of Disseminate Lupus Erythematosus (1938 Through 1947)*

Data	Type of Disseminate Lupus Erythematosus		
	Chronic (23 Cases)	Subacute (77 Cases)	Acute (32 Cases)
Women, per cent	83	87	91
Onset as discoid type, per cent	30	17	6
Average age at onset, years	33	33	27
Average age at onset of dissemination, years	34	36	28
Prodromal symptoms, per cent	5	14	41*
Sensitivity to light, per cent	56	40	22
Arthralgia or arthritis, per cent	43	71	91
Anemia (less than 4,000,000 erythrocytes per cubic millimeter or less than 12 Gm. hemoglobin), per cent	35	54	91
Leukopenia (less than 5,000 leukocytes per cubic millimeter), per cent	30	67	81
False-positive flocculation or Wassermann reaction, per cent	17	25	44
Renal irritation, nephrosis or nephritis, per cent	39	69	100
Albumin	39	56	100
Erythrocytes	9	34	81
Casts	4	17	69
Deaths attributable to the disease, per cent	4	35	84†

* Five patients had no cutaneous lesions when first seen here (lupus erythematosus without cutaneous lesions).

† Five patients were still alive at last report. One had completely recovered, having been followed for five years with no evidence of the disease for eighteen months. One was a semi-invalid followed for thirteen and one-half years after the onset of disease, seven and one-half years after dissemination. Efforts to follow up 3 patients were unsuccessful, and the chances are that these persons are dead.

TABLE 3.—*Analysis of Other Laboratory Data in One Hundred and Thirty-Two Cases of Disseminate Lupus Erythematosus (1938 Through 1947)*

Data	Type of Disseminate Lupus Erythematosus					
	Chronic		Subacute		Acute	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Sedimentation rate, mm. per hour	20		70		31	
Normal, 0-20		35		14		0
Mildly increased, 21-40		25		16		3
Moderate, 41-60		25		21		19
Rapid, 61 or more		15		49		78
Serum proteins (total)	2		33		22	
Normal, 6-8 Gm. per 100 cc. serum		50		79		64
Total proteins, less than 6 Gm. per 100 cc. serum		50		6		32
Total proteins, more than 8 Gm. per 100 cc. serum		0		15		4
Albumin-globulin ratio	2		31		18	
Normal, 1.5:1-3:1		50		16		6
Ratio less than 1.5:1		50		84		94

We have kept the classification employed by O'Leary, which is similar to that previously used by Madden, of dividing cases of disseminate lupus erythematosus into chronic, subacute and acute types.

7. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948.

The chronic type has also been termed the "generalized discoid" type, or, in other words, discoid lupus erythematosus in which lesions occur elsewhere than on the face. Chronic discoid and generalized disseminate lupus erythematosus are usually regarded as cutaneous diseases, with few, if any, constitutional symptoms. One can see, however, from tables 1, 2 and 3 that constitutional symptoms are present in a number of cases of chronic disseminate lupus erythematosus. The classification of what most writers term "disseminate lupus erythematosus" into subacute and acute phases is a rather arbitrary one, based on the degree of severity of the systemic findings and on a period of observation. The classification in the original group resulted from unpublished studies by O'Leary and Rogin and discussion by one of us (H. M.) with O'Leary as to where to group certain cases. A similar plan was carried out in the analysis of the recent series of 132 cases, an attempt being made to maintain the same criteria in regard to classification.

ANALYSIS OF CLINICAL AND LABORATORY FINDINGS

We believe a brief discussion of the similarities and discrepancies between tables 1 and 2 to be of value. Some of the discrepancies are obviously mathematical, as there are too few cases in the various groups for the data to be presented accurately on a percentage basis. Some of the discrepancies undoubtedly arise from the changing concept of the disease, a difference in attitude including the fact that internists as well as the members of the section on dermatology at the clinic have become more lupus erythematosus-conscious, as a result of which there are many more cases reported in the later series, especially of the acute disseminate form, in which cutaneous manifestations were minimal or transitory. Increasing predominance of the disease in women in the recent series fits in with reports of series elsewhere in which an incidence as high as 95 per cent has been reported in women (Baehr, "Oxford Medicine"). The finding of only 6 per cent of the acute cases in which the disease started as the chronic discoid type instead of the observation of 33 per cent in which it did so in the older series is probably explainable on the basis of the present recognition of acute fulminating forms of the disease with minimal cutaneous manifestations, which forms previously would have been considered chronic. This observation does not imply, however, that chronic discoid and acute disseminate lupus erythematosus are two different diseases, as some writers would maintain, because all transitions may be seen both clinically and pathologically in cutaneous lesions. This situation is comparable to that observed in sarcoidosis, in which there may be lesions limited to the skin or limited to the bones, lungs,

lymph nodes and other organs and in which all combinations in extent and severity of the process may occur.

The diagnosis of lupus erythematosus without cutaneous manifestations is difficult to make. All the patients whose cases are included in table 2 presented evidence of cutaneous lesions at some time during the course of the disease. There are approximately 6 additional cases that were encountered in the period from 1938 through 1947 in which the diagnosis of lupus without cutaneous lesion was entertained because of various systemic manifestations and laboratory findings. In 2 of these cases, further observations suggested the diagnosis of periarteritis nodosa and dermatomyositis, respectively, and in 4 cases a diagnosis of disseminate lupus erythematosus seemed justifiable, there being lupus erythematosus cells in sternal marrow obtained by aspiration in 3 cases.

There can be no question that bona fide cases of lupus without cutaneous lesions have been reported in the literature with or without their having had the features of the Libman-Sacks syndrome. A patient who might be classified in this group and who is not included in this series was at the clinic in February 1948.

She was a woman, aged 33, who had had recurrent arthralgias for eight years, had complained of abdominal pain and menorrhagia in January 1947 and had exhibited edema of the feet and ankles and decreased urinary output in May 1947. In August 1947 she had had furuncle-like lesions that were generalized but worse on the extremities than on other parts of the body and which cleared with antibiotic treatment. Later, there had been a recurrence of a few of the lesions on the feet. When seen at the clinic, the patient apparently had no cutaneous lesions of any sort. It is possible that the lesions that she had could have been purpuric, ulcerative or bullous lesions of lupus erythematosus, but this would seem unlikely. The patient had been hospitalized from May 1947 because of severe anemia. Reactions to transfusions had developed, and she had had a progressive downhill course with much edema, ascites and septic temperature. The patient died early in 1948, five days after admission to the hospital with a sudden onset of severe headache and dyspnea. Laboratory findings before death included albumin and erythrocytes in the urine and a blood urea of 118 mg. per hundred cubic centimeters. The concentration of hemoglobin was 5.4 Gm. per hundred cubic centimeters of blood; erythrocytes numbered 3,160,000 and leukocytes 9,800 per cubic millimeter of blood. The sedimentation rate (Westergren method) was 141 mm. per hour; the Kline reaction was 1 plus and the Kahn, 3 plus; the total proteins measured 3.9 Gm. per hundred cubic centimeters of serum, and the albumin-globulin ratio was 1.6:2.3. The clinical diagnosis was chronic glomerulonephritis with edema, ascites and hypertension (the blood pressure was 180 mm. of mercury systolic, and 105 mm. diastolic). Postmortem examination failed to reveal evidence of glomerulonephritis but showed pronounced wire loop changes in the kidneys, such as are frequently associated with lupus erythematosus, and also a nonbacterial verrucous endocarditis and a perisplenitis. This case is reported, therefore, simply to illustrate the difficulties of diagnosis but, in retrospect, should probably be classified as one of lupus without cutaneous lesions.

To continue with the comparison of tables 1 and 2, the 22 per cent incidence of sensitivity to light found in the acute disseminate cases corresponds with recent reports in the literature that a light-sensitive factor does not necessarily predominate and need not even be considered a factor in acute disseminate cases. There still remain, however, many cases in which dissemination of chronic discoid or subacute disseminate lupus erythematosus has resulted from exposure to light.

We purposely omitted from table 2 any figures regarding lesions of the mucous membranes, incidence of fever and the percentage of patients with infected tonsils because the association of these conditions is generally accepted. Some of the changes regarding the percentage of patients with leukopenia result from our acceptance in the later series of 5,000 leukocytes per cubic millimeter, rather than 4,500 leukocytes per cubic millimeter, as the lower limit of normal (a value which apparently is now accepted in hemocytologic texts). The increase of false-positive serologic reactions seen in table 2 may be explained on the basis of the fact that in practically all the cases in the recent series not merely a single serologic test for syphilis, but a battery of four tests, including the Kahn, Kline, Hinton and Kolmer tests, was given. This was not usually true of the first series. As was remarked, however, in the chapter by one of us (H. M.) in "Oxford Medicine," results of serologic tests for syphilis seemed to become increasingly positive in a given person, the increase depending on the acuteness of the disease. In several cases in the acute disseminate group in the recent series the reaction of all four tests was strongly positive. Disseminate lupus erythematosus should definitely be grouped with the diseases causing false positive serologic reactions.

In table 1 evidence of renal irritation, nephrosis or nephritis was based on a rather critical analysis of the various urinary findings; however, it was felt advisable simply to tabulate the urinary data in the present series. Observations regarding elevated blood urea and hypertension with or without renal disease remained in the recent series essentially as given in the chapter in "Oxford Medicine" and summarized in papers by Keith and Stickney,[2] as part of a symposium, but are subject to further analyses.

In regard to deaths attributable to the disease, in table 1, as was originally reported in "Oxford Medicine," 2 patients of those with the acute form were alive. Both of these patients died subsequently, although 1 remained alive for eight years after the onset of the acute disseminate lupus erythematosus. The footnote on table 2 regarding deaths in the recent series is self explanatory. Though duration of life in the group with the acute form of the disease may be a matter of only a month and death usually occurs within a year, there are increasing but isolated cases reported in which the disease has persisted

for from five to eight or more years, these cases including some noted by the Mount Sinai group.[8] In the group with subacute disseminate lupus erythematosus, as indicated in table 1, there was one subsequent death. We were able to follow up a majority of this group through letters of inquiry or further observation of the patient.

Table 3, which gives an analysis of some of the other laboratory data in the recent series of patients with disseminate lupus erythematosus, is self explanatory. In some instances, so few examinations were performed that the percentage figures are of little significance. In general, the sedimentation rate increased and the albumin-globulin ratio became reversed as the condition became more acute and severe. (There were no determinations made of euglobulins.) Thus, in the cases in which there were the highest sedimentation rates and reversal of the albumin-globulin ratio there was likely to be the greatest degree of false positive serologic reaction, without, however, our being able to attach any diagnostic significance to this phenomenon.

Other laboratory procedures were performed in too small a series of cases to permit presentation in tabular form. Positive blood cultures were obtained in 2 of 31 instances. A green-producing streptococcus was obtained on blood culture in 1 case of acute disseminate lupus erythematosus, and a staphylococcus was obtained in 1 case of subacute disseminate lupus erythematosus.

In 13 cases, determination was made of the total 17-ketosteroids present in a twenty-four hour specimen of urine. In 1 case of acute and in 1 case of the chronic disseminate type of lupus erythematosus, ketosteroids measured less than 4 mg. per hundred cubic centimeters for twenty-four hour specimens. In a series of 11 cases of the subacute type of lupus erythematosus, 5 women and 1 man had values of less than 4 mg. for twenty-four hours, whereas 5 women had values of more than 4 mg. in twenty-four hours. The amount of 17-ketosteroids, therefore, seemed to be without diagnostic significance and probably was indicative only of the toxic manifestation of a debilitating disease.

Aspiration of sternal marrow was attempted in 26 cases. Of 7 cases classified as of acute disseminate lupus erythematosus, aspirated sternal marrow was reported as positive for lupus erythematosus cells in 5 cases. In 1 case observations were suggestive of lupus erythematosus cells, and in 1 case the attempt at aspiration was unsuccessful. The 5 patients in this group who had lupus erythematosus cells and the 1 in whose marrow there were cells resembling lupus erythematosus cells are known to have died. There were 18 patients with subacute disseminate lupus erythematosus who had aspirations of sternal marrow.

8. Baehr and Pollack.[4] Klemperer.[5]

For 12 of these the aspirated marrow was negative for lupus erythematosus; for 3 it was positive, and for 1 it was suggestive. One patient had two aspirations, lupus erythematosus cells not being demonstrated in the first specimen and leukemic reticuloendothelial cells being reported in the second. Aspiration of sternal marrow was unsuccessful in 1 patient on six different attempts. Sternal aspiration was negative for lupus erythematosus cells in 1 case of chronic disseminate lupus erythematosus. Lupus erythematosus cells, as described by Hargraves and his associates, appear to predominate in cases of disseminate lupus erythematosus in which the disease is active or increasing and are not demonstrable, as a rule, if the condition is quiescent. So far, lupus erythematosus cells have not been reported as occurring in any other condition except in 1 case of multiple myeloma.[9] Further observation of a large series, however, will be necessary for their status and diagnostic significance to be determined.

Analysis or comparison of various systemic manifestations found in the two series of cases does not show any fundamental variations of the recent series from those reported for the first series in "Oxford Medicine" or from those cited in recent articles in the literature, which are quoted in recent reviews.[10] Reports of ocular findings, as seen at the clinic and elsewhere, were recently reviewed by Wagener.[11] Gastrointestinal symptoms have been minimal in the present series of 132 cases. We should like, however, to emphasize that there have been several cases with symptoms which involved the central nervous system and which were not terminal manifestations but were encountered early in the course of acute or subacute disseminate lupus erythematosus. The symptoms in 1 case included headaches, choked disks and palsy of the face, with evidence at postmortem examination of endarteritis of the cerebral vessels. In another case, there were cerebrothrombosis, convulsions, aphasia and weakness in a girl aged 16 years, who also had evidence of anemia, an increased sedimentation rate, renal irritation and false positive serologic reactions. Another patient had nervous irritability and development of a cerebral accident, with convulsions and euphoria; when seen a year later, she had typical lesions of lupus erythematosus of the scalp and body, and aspirated bone marrow was positive for lupus erythematosus cells. Although the tendency has been to focus attention on the cardiac, renal, hepatic, splenic or arthritic involvement in lupus erythematosus, it is evident that any organ in the body may be involved in the process.

9. Hargraves, M. M.: Personal communication to the authors.

10. Baehr and Pollack.[4] Klemperer.[5] Hench and others.[6] Ormsby and Montgomery.[7]

11. Wagener, H. P.: Retinal Lesions in Acute Disseminate Lupus Erythematosus, Am. J. M. Sc. **211**:240-244 (Feb.) 1946.

PATHOLOGIC FACTORS

The pathogenesis of lupus erythematosus and allied conditions has been discussed in recent articles by the Mount Sinai group in New York, and detailed reasons have been given for regarding these conditions as collagenous diseases associated primarily with fibrinoid degeneration of collagen. Baehr and Pollack, and Klemperer, though they called attention to fibrinoid degeneration in lupus erythematosus and scleroderma, recognized that these conditions are distinct from one another and also that they are not related to rheumatic fever, rheumatoid arthritis, serum sickness, periarteritis nodosa or thromboangiitis obliterans, in which similar collagenous changes may be seen on pathologic examination. In cases in which postmortem examinations were performed in the original series of 154 cases and on which Stickney's observations were based, wire loop changes in the kidneys, including hyaline and fibrinoid degeneration in the basement membrane of the glomerular capillaries, were relatively absent. There was no clearcut case of nonverrucous bacterial endocarditis, although subsequent study of 1 of 6 cases changed the diagnosis from bacterial to nonbacterial endocarditis. Postmortem findings in some cases of the second series, as well as in cases in the first series, were reviewed by Correa.[12] It would appear not only from our own records but also from other reports in the literature that in an increasing number of cases, possibly half of the reported cases with autopsy, there is observed fibrinoid degeneration of the collagen, including the vascular changes previously emphasized by Klemperer and his associates in regard to changes occurring in the kidneys and heart. Similar changes are much less frequent in the spleen and other organs. Whether these changes are primary or of toxic nature remains open to debate.

One of us (H. M.) has written several articles on the cutaneous changes in disseminate lupus erythematosus and has found little evidence of collagenous change, including fibrinoid degeneration and obliterative changes in superficial vessels in the skin. We have reviewed cutaneous specimens for biopsy of 96 lesions of disseminate lupus erythematosus, 25 lesions from 22 cases of chronic types, 53 lesions from 41 cases of subacute types and 18 lesions from 16 cases of acute types. Details of these studies will be the subject of a subsequent report.[13] This series included specimens for biopsy on

12. Correa, D. H.: Pathology of Disseminated Lupus Erythematosus with Special Reference to the Vascular Changes, Thesis, Graduate School of the University of Minnesota.

13. These will appear in a thesis to be submitted by Dr. McCreight to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Dermatology.

which previous reports were based. Special stains for connective tissue were employed in many cases.

Briefly, we were able to find alteration of collagen, including fibrinoid changes in the walls of the vessels in the skin and around the connective tissue in the cutis, in less than one fourth of the cases, respectively, of chronic, subacute and acute disseminate lupus erythematosus. In only 1 or 2 cases in each of the groups were there collagenous changes comparable in extent to those usually seen in the so-called wire loop lesions in the kidneys. In the rest of the cases in which fibrinoid degeneration could be demonstrated, it was minimal and no greater than is seen in many other chronic inflammatory infectious diseases of the skin. We submitted all sections showing fibrinoid changes to Dr. Bennett of the section on pathologic anatomy of the clinic, who examined them independently and also found very slight amounts of changes, including fibrinoid changes, in the blood vessels.

There is no question that in disseminate lupus erythematosus the superficial capillaries are dilated and often the walls of both venules and arterioles are edematous and also that there is destruction of both connective and elastic tissue by the inflammatory reaction in the cutis. Basophilic degeneration and merging of collagen and elastic fibers to form collacin, as one of us (H. M.) previously emphasized, are seen only in lesions from the exposed parts of the body and then are not predominant in the disseminate group, as these changes may occur in the discoid group. We still believe that the histopathologic diagnosis of disseminate lupus erythematosus can be made in the majority of cases if a specimen for biopsy is taken from a lesion that has not been subject to treatment and that is at least of several weeks' duration. All transitions between chronic discoid and acute disseminate lupus erythematosus, as they were illustrated in previous papers, were again encountered.

The Mount Sinai group in New York have stated that fibrinoid degeneration of collagen is not a pathologic process of sufficient specificity to serve as a reliable common denominator for classification of diseases. The minimal changes in the collagen in cutaneous manifestations of disseminate lupus erythematosus raise the question as to how important a role collagenous disease plays in lupus erythematosus. The skin, of course, is one of the organs most richly endowed with collagenous material. On the other hand, we are heartily in accord with the Mount Sinai group regarding emphasis on collagenous disease in scleroderma. In scleroderma, there are obliterative changes in the vessels with fibrinoid degeneration of the collagen and diffuse proliferative and degenerative changes in the collagen throughout the cutis.

ETIOLOGIC FACTORS

We do not wish to repeat all the multiple etiologic factors to which disseminate lupus erythematosus has been attributed. In both the old and the recent series, tuberculosis played an insignificant role, although one may encounter an occasional case in which a tuberculous infection may be superimposed on disseminate lupus erythematosus and result in death. We agree with Baehr and his associates that the concept of lupus erythematosus being of tuberculous origin should be abandoned, although this concept apparently still persists in some of the European writings.

There have been several recent articles in the literature dealing with the effect of pregnancy and endocrine disturbances on lupus erythematosus. We have seen acute lupus erythematosus develop after normal pregnancy and run a rapidly fatal course, and we have had patients who showed temporary improvement after oophorectomy. After review of cases of various types of disseminate lupus erythematosus associated with pregnancy, we believe that pregnancy may, at the most, be merely a contributing factor and we agree with O'Leary, who stated in a discussion of Baehr and Pollack's paper that "therapeutic castration of women who have disseminate lupus erythematosus has been valueless in my experience." Baehr,[4] in a discussion of his paper with Pollack, also stated that treatment of disseminate lupus erythematosus with testosterone propionate or castration in women has not materially altered the course of the disease and that he had not seen any evidence of endocrine disorder in men having disseminate lupus erythematosus. Baehr and Pollack stated the belief that the predominance of the disease in women merely represents a sex predisposition similar to the predisposition for men seen in thromboangiitis obliterans. They also express opposition to the acceptance of an allergic basis for lupus erythematosus. There were no patients in either of our series in whom an allergic factor predominated unless we include those patients who were sensitive to light.

We have already stated our views against regarding lupus erythematosus as primarily a collagenous disease. We believe that there may be multiple etiologic factors and that toxic changes of unknown nature may predominate. In other words, the etiology of lupus erythematosus remains to be determined.

DIAGNOSIS

The diagnosis of localized discoid and chronic disseminate lupus erythematosus is usually readily made on the basis of the clinical appearance of the lesions. In many cases of subacute or acute disseminate lupus erythematosus, small areas with characteristic scaling and plugging may be recognized. The combination of erythematous involvement of the face and finger tips is also almost pathognomonic.

It is in the more acute forms, in which there may be only a transitory erythema, that the diagnosis becomes more difficult, and this erythema may not necessarily involve the face. Sometimes there is transient purpura, or there may be hemorrhagic lesions. Diagnosis becomes more difficult when there are no cutaneous manifestations. It must be borne in mind that lupus erythematosus, especially the acute disseminate type, may affect any organ in the body. The diagnosis is to be seriously entertained even without cutaneous lesions when several of the following combinations or signs occur: arthralgias or arthritis; cardiac symptoms; evidence of renal irritation or nephritis associated with malaise; a septic type of temperature; leukopenia and secondary anemia; an increased sedimentation rate; false-positive reactions in Wassermann and flocculation tests; albumin, erythrocytes and, at times, casts in the urine; and reversal of the albumin-globulin ratio. To this group we may add tentatively the demonstration of so-called lupus erythematosus cells on sternal aspiration. One must also keep in mind that symptoms referable to the gastrointestinal tract or to the central nervous system occur in some cases, as do ocular changes.

It now appears that most cases of the Libman-Sacks syndrome, including nonbacterial verrucous endocarditis, wire loop lesions in the kidney and perisplenitis, or more than one of these manifestations, are essentially cases of disseminate lupus erythematosus. Nonbacterial verrucous endocarditis, however, may occur in a good many other conditions entirely unrelated to lupus erythematosus.[14] Conversely, many cases of disseminate lupus erythematosus do not reveal the features of the so-called Libman-Sacks syndrome.

Disseminate lupus erythematosus may be confused with dermatomyositis, and there are cases reported in the literature in which the two conditions are supposed to be associated in the same person. We had 1 case of subacute disseminate lupus erythematosus in which, four years after the onset of the disease, dermatomyositis apparently developed, with pronounced weakness and wasting of the major muscles of the trunk, although a specimen for biopsy from the skin still revealed the histologic picture of subacute disseminate lupus erythematosus. Biopsy of a specimen of the muscle revealed dermatomyositis. As a rule, lupus erythematosus and dermatomyositis can be distinguished. The cutaneous lesions of dermatomyositis, although histologically simulating those associated with acute disseminate lupus erythematosus, show merely a toxic dermatitis and fail to reveal liquefaction degeneration of the basal cell layer, keratotic plugging and other features of lupus erythematosus. Clinically, in dermatomyositis

14. Kernohan, J. W.: Personal communication to the authors.

there is likely to be more edema about the eyelids, with a heliotrope-like coloring, than in lupus erythematosus. Weakness and atrophy of the muscles are not prominent features of lupus erythematosus but are characteristic of dermatomyositis. From the laboratory aspects, dermatomyositis is not associated, as a rule, with leukopenia, anemia or false positive serologic reactions; on the other hand, it is associated with creatinuria.

Distinction of early or mild forms of disseminate lupus erythematosus from cases of sunlight dermatitis (eczema) must be made on the basis of concomitant findings. In patients who have a sensitivity to sunlight various degrees of dermatitis, as well as decided malaise and constitutional symptoms, may develop after exposure to the sun, but this group of patients should be sharply distinguished from patients with lupus erythematosus who also may be sensitive to the sun.

TREATMENT

There is no satisfactory treatment of disseminate lupus erythematosus. Avoidance of exposure to the sun, prolonged rest in bed and various supportive measures directed to the constitutional symptoms are indicated. We have not found the use of sulfonamide compounds or penicillin to be of value.

SUMMARY AND CONCLUSIONS

Disseminate lupus erythematosus, especially the acute and subacute types, must be regarded as a systemic disease. Cutaneous manifestations may be minimal or even absent. Analysis is given of 154 cases of disseminate lupus erythematosus encountered up to 1938 and of 132 cases of disseminate lupus erythematosus encountered from 1938 through 1947. The following observations are worthy of emphasis. False positive reactions in Wassermann or flocculation tests occur in increasing percentage according to the acuteness of the disease, as also do increase of the sedimentation rate and reversal of the albumin-globulin ratio. It would appear that the presence of the so-called lupus erythematosus cells in sternal aspirations of bone marrow is of diagnostic and prognostic value in cases of acute disseminate lupus erythematosus with or without cutaneous lesions. However, a large series of cases should be studied and further observations should be made in this regard. Studies of the histologic changes in the skin in various types of disseminate lupus erythematosus show only minor changes in the collagen or fibrinoid degeneration in the walls of the vessels. We should prefer, therefore, not to regard lupus erythematosus primarily as a collagenous disease but to continue to regard the cause as unknown. We found little evidence to support the

theory of an endocrine or an allergic origin. There is, at present, no satisfactory form of treatment other than rest in bed, avoidance of exposure to sunlight and general supportive measures.

ABSTRACT OF DISCUSSION

DR. ROBERT L. GILMAN, Philadelphia: This is a remarkable series of cases that Drs. Montgomery and McCreight have just reported on. It is unusual in the number of patients, the almost exhaustive analyses and the opportunity given for one to compare two consecutive series studied similarly and observed by the same groups. The noted differences between the two series are no less surprising than the obvious similarities.

I shall not attempt to comment on these worker's histologic studies nor on the findings at autopsy in their variance from those noted by the Mount Sinai group other than to compliment Drs. Montgomery and McCreight on their level appraisals, their unwillingness to accept unsubstantiated theories and the avoidance of fanciful conclusions. The variation between their findings and those of the Eastern group is not as great as it at first appears—the geographic source of their respective patients may be at least one reason for an apparent difference. This particular suggestion but recently came to my attention after I had encountered 3 successive cases of acute dissemiated lupus erythematosus in young Polish men in Philadelphia. The gross morbid changes were of the character and extent described by Baehr and Pollack and Klemperer.

It is possible that too much stress has been placed on the importance of collagen or that fibrous tissue structure has been endowed with unproved functions and significance. It is known that this structure is of the widest distribution throughout the body, with obvious functions of support, strength and compartmentation. Other functions have been concluded. However, an increasingly recognized number of disease states characterized by collagen alteration have been grouped together because of these changes, and were this sole common finding the linkage would be tenuous indeed. Commoner examples of diffuse collagen diseases, in addition to disseminated lupus erythematosus, are acute rheumatic fever, scleroderma, dermatomyositis and periarteritis nodosa. In addition to collagen changes they have other features in common, including the predilection in at least three for persons in the younger age group and for women. They diverge greatly in etiologic possibilities—I assume that none of these conditions has a single incontrovertible cause—and again this observation is common to all five conditions.

Other features that may hold more promise in solving the problem of the causation of disseminated lupus erythematosus are the bone marrow changes, the altered albumin-globulin ratios with the consequent serologic phenomena, and, most recently, the recognition of the "lupus erythematosus" cell. It may be in any one of these that we may find the clue to the etiology. The observations contained in the charts of the two series of the increasing occurrence of prodromal symptoms, fever, increased sedimentation rates and arthralgia toward the acute phase will add evidence to the ultimate recognition of the cause. Parenthetically, it can be added that these same clinical and laboratory signs are sufficiently delineatory to permit the dropping of the qualifying term "arbitrary" from the classification of O'Leary and Madden.

I do not believe that one can quite discard the endocrine role in etiology by dismissing with the term "sex predisposition" the overwhelming incidence among younger women. Nor can the importance of previous banal infections and the concomitant chemotherapy that appear frequently in the histories of these patients

be disregarded. Finally, there is the possible role of heavy metals, as has been commented on by a member of this association.

The solving of the problem of any one of the diffuse collagen diseases may well be the key to all.

DR. JOHN F. MADDEN, St. Paul: I had the opportunity to read Dr. Montgomery's paper. It represents a tremendous amount of work on the largest number of cases of this disease studied by one author. I should like to emphasize the following points. The Hargrave, or lupus erythematosus, cell is most numerous and most often found in acute cases. This fact is a great diagnostic aid, especially in cases of lupus erythematosus without cutaneous manifestations. The high incidence of false positive serologic reactions in cases of acute lupus erythematosus should be constantly kept in mind. Many autopsies have been made in cases of acute lupus erythematosus, but I was unable to find a record of a single autopsy in all the hospitals in St. Paul and Minneapolis made in cases of chronic lupus erythematosus in which there was death from any cause. The disease wasn't even mentioned on autopsy records. A careful study should be made of the autopsy findings in cases of chronic lupus erythematosus. In some cases of acute lupus erythematosus there is extensive muscle damage, which can be observed at biopsy. My associates and I will report on this subject in detail later. I enjoyed Dr. Montgomery's paper very much.

DR. H. J. TEMPLETON, Oakland, Calif.: Acute disseminated lupus erythematosus is an edema-producing disease. The edema of the face paints a rather typical clinical picture. Edema of the brain accounts for many of the nervous symptoms, even convulsions and coma. Edema of the lungs occurs in terminal cases. Edema of the abdominal organs probably accounts for the abdominal pain which occasionally is found in this disease.

A physician's son, with the fulminating type of the disease, had such intense abdominal pain that a surgical consultant wished to do an exploratory laparotomy. It was with considerable difficulty that I convinced the physician-father and the surgeon that the pain was caused by the lupus erythematosus and that surgical intervention was contraindicated. I had previously seen the same diagnostic problem in a young woman, in whose case autopsy was performed. The extremely acute edema of nearly all the abdominal viscera explained her severe abdominal pain.

I know of no absolute criterion for differentiating the pain of acute disseminated lupus erythematosus and that caused by a "surgical abdomen." The most important point is the knowledge of the dermatologist that acute disseminated lupus erythematosus can produce such pain. The surgeon generally does not have this knowledge.

DR. MAURICE J. COSTELLO, New York: I have recently had the opportunity to study a woman 31 years of age in whom acute lupus erythematosus of the disseminate type developed. She had had a splenectomy in 1945 for thrombopenic purpura.

For some time thereafter she complained of fatigue and pain and swelling of the finger joints. Within a month or two an eruption appeared which was generalized, roughly symmetric and intensely pruritic, the lesions occurring in groups of papules and vesicles.

When I first saw the patient, in August 1947, she stated that the eruption had been present uninterruptedly for about eighteen months. The eruption was that of dermatitis herpetiformis. Sulfapyridine was not prescribed because of her past history of purpura, the presence of splinter hemorrhages of the sides of the terminal

phalanges and the presence of albumin in her urine. Potassium arsenite solution U. S. P. (Fowler's solution) was prescribed because of the persistence of this severe, generalized, pruritic eruption. The cutaneous manifestations of dermatitis herpetiformis disappeared almost completely under this medication.

In September 1947 the patient exposed herself to sunlight, covering all parts of her body except the upper part of her chest. Within a week there developed about a dozen pea-sized to dime-sized, elevated, erythematous lesions of lupus erythematosus on the V area of her chest. They remained unchanged for three months.

I presented her at the November 1947 meeting of the New York Dermatological Society, at which time she exhibited an eruption of dermatitis herpetiformis undergoing involution, as well as lupus erythematosus.

On Dec. 8, 1947, she had an extraction of an abscessed tooth, which was followed by fever, malaise and pains in the joints. On about March 1, 1948, she presented the typical picture of acute lupus erythematosus of the disseminate type, with all the other classic signs and symptoms accompanying this disease, such as hyperpyrexia, pericarditis and endocarditis.

About two or three weeks before her death the eruption of acute lupus erythematosus underwent almost complete involution, and a generalized, malignant, vesicular-bullous-pemphigoid type of erythema multiforme, indistinguishable from Stevens-Johnson disease, as also described by Klauder and later by me, with ophthalmia and oral and genital involvement, assumed the dominant role.

The patient died on April 14, 1948. I will not give the details of the post-mortem investigation other than that an anticipated golf-ball-sized remaining accessory spleen was discovered, in addition to pericarditis with organization, pleural effusion and numerous miliary lesions throughout the lungs.

Dr. George Baehr, who saw this patient, stated that he had seen 3 cases of acute lupus erythematosus of the disseminate type following splenectomy for thrombopenic purpura. Did the clinical manifestations, cutaneous and visceral, of this patient all stem from an original infection (probably streptococcic) masquerading in different guises depending on the increasing vulnerability of the host? Was the thrombopenic purpura the first manifestation of her acute lupus erythematosus?

DR. WILLIAM H. GOECKERMAN, Los Angeles: I also had the opportunity to look at Dr. Montgomery's paper, and I should like to assure you that the amount of work that it represents is phenomenal. Drs. Montgomery and O'Leary have had an unusual opportunity in recent years to study this particular subject, and it is a pleasure to hear this paper. Many of you know that I have been interested in the subject for a good many years. I was glad to hear that Dr. Montgomery still emphasizes the general systemic findings, not only in the acute type but also in the subacute form. Another point is that he still holds that, histologically as well as clinically, one can see all transitions from the chronic to the acute type. To all these points I can heartily subscribe through continued personal study. It should again be emphasized that these patients are supersensitive, not only to sunlight, but to all minor interference, including the administration of drugs. Small doses in treatment are often much better than larger doses. There are many systemic symptoms, including confusing abdominal pains. I was extremely glad to hear this paper.

DR. HARRY ARNOLD JR., Honolulu, Hawaii: I should like to suggest that the abdominal pain which sometimes occurs in these patients may have the same cause as that associated with Henoch's purpura abdominalis (nonthrombopenic purpura), and that in differentiation of this pain from that caused by acute surgical lesions of the abdomen, it may be helpful to determine the Weltmann coagu-

lation band. This band should be shifted to the left, from a normal value of 6 to 4 or 2 or even 0, in acute exudative disease of any sort; but it is shifted to the right, to 7 or 8, in almost all cases of disseminated lupus erythematosus. Also, the pain in these cases is likely to be relieved very little by morphine and rather promptly by ephedrine, epinephrine or even antihistaminic drugs. Dr. Costello made a remark that interested me particularly. My colleague, Dr. Harold Johnson, has observed in a number of cases of this disease that splenectomy (originally performed in 2 cases as a life-saving measure, to combat an associated thrombopenic purpura) was followed by prompt remission of the disseminated lupus. I have undertaken this operation in 2 cases, in neither one of which the patient had thrombopenia, and both patients have experienced a remission; though 1 subsequently had a relapse, she is still getting along fairly well and has had no recurrence of leukopenia.

Dr. Hamilton Montgomery, Rochester, Minn.: I wish to thank the discussers and I am essentially in accord with their emphasis on various other aspects of the disease, which time did not permit discussion of. Because of the predominance of acute disseminate lupus erythematosus in young women, it was thought a cure might be obtained by therapeutic castration, but so far this treatment has been valueless. We have seen no benefit from the use of testosterone. There is no satisfactory explanation at present for the predominance of the disease in women any more than there is for the predominance of Buerger's disease (thromboangiitis obliterans), in men. Some years ago, we studied a group of our cases for evidence of poisoning by heavy metals, including lead, with negative results. I was glad to have the point brought up about muscle changes in disseminate lupus erythematosus. The majority of cases with muscular atrophy and weakness of the major muscles have proved to be cases of dermatomyositis. We recently had 1, however, which histologically and clinically in the beginning was one of disseminate lupus erythematosus and in which clinical features of dermatomyositis subsequently developed, while the cutaneous changes remained those of lupus erythematosus and not the toxic changes in the skin seen in dermatomyositis. Unfortunately, no specimen for biopsy of the muscle was taken. In the older series of cases, there were several cases of disseminate lupus erythematosus in which abdominal pain was an outstanding complaint. Dr. Goeckerman referred to these cases in a paper written many years ago. In regard to Dr. Templeton's suggestions regarding edema in the brain, in 2 of the cases referred to in the paper with symptoms of brain tumor or other neurologic disturbances postmortem examination was done, definite inflammatory changes in the brain being observed in both cases. In regard to Dr. Costello's remarks regarding splenectomy, it is true that patients with disseminate lupus erythematosus may be allergic in a broad sense. In acute cases one must be cautious regarding the removal of even one infected tooth. It is important first to obtain a state of temporary remission or quiescence of the disease if possible before removing any foci of infection. Various types of purpura have been reported in a few cases but were an uncommon manifestation in our group and were more likely to be terminal manifestations of the disease.

CUTANEOUS LESIONS OCCURRING IN THE COURSE OF STREPTOMYCIN THERAPY

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DERMATITIS in the course of streptomycin therapy was noted by Heilman and associates in 1945.[1] These authors warned that, though such cutaneous lesions do not call for cessation of treatment with streptomycin, it is important for one to be on the alert for severe dermatitis. In the report on streptomycin by the National Research Council,[2] 49 cutaneous eruptions were mentioned. These were erythematous, urticarial, maculopapular or hemorrhagic. Steiner and Fishburn [3] reported 7 cases of rashes occurring during the administration of streptomycin. They stated the belief that these reactions are not toxic but allergic. In their report to the Council on Pharmacy and Chemistry [4] the Study Units of the Veterans Administration, the Army and the Navy stated that in 18 per cent of 223 cases in which 2 Gm. of streptomycin was given daily a pruritic, erythematous, maculopapular skin eruption appeared after about ten days of treatment. The pruritus was easily controlled by treatment with diphenhydramine hydrochloride (benadryl hydrochloride®), and the eruption disappeared with continued treatment. In 1.4 per cent of the cases in the same series, a severe exfoliative dermatitis appeared.

In November 1947 Canizares and Shatin reported the first case of dermatitis venenata due to streptomycin.[5] Shortly thereafter, Rauch-

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1. Heilman, D. H.; Heilman, F. R.; Hinshaw, H. E.; Nichols, D. R., and Herrell, W. E.: Streptomycin: Absorption, Diffusion, Excretion and Toxicity, Am. J. M. Sc. **210**:576-584 (Nov.) 1945.

2. Keefer, C. S.: Streptomycin in the Treatment of Infections, J. A. M. A. **132**:70-76 (Sept. 14) 1946.

3. Steiner, K., and Fishburn, G. W.: Cutaneous Eruptions from Streptomycin, Arch. Dermat. & Syph. **56**:511-516 (Oct.) 1947.

4. Effects of Streptomycin on Tuberculosis in Man, report of Council on Pharmacy and Chemistry, J. A. M. A. **135**:634-641 (Nov. 8) 1947.

5. Canizares, O., and Shatin, H.: Dermatitis Venenata Due to Streptomycin, Arch. Dermat. & Syph. **56**:676-677 (Nov.) 1947.

werger and associates[6] reported 6 additional cases of dermatitis venenata in nurses who had had prolonged contact with streptomycin. In all cases there was an initial erythema followed by pruritus and a papulovesicular eruption, and, in addition, in 5 cases there was edema of the lids, associated with pruritus and photophobia. Recently, we have been informed of a nurse at the Veterans Administration Hospital, Livermore, Calif., who, after prolonged contact with streptomycin, acquired a true exfoliative dermatitis.[7]

In the course of the past two years 137 patients have been treated with streptomycin at this hospital. Various lesions of the skin and mucous membranes have been seen in these patients and in nurses who have handled the drug. The frequency and severity of the dermatologic complications occurring in patients vary with the dosage.

The commonest cutaneous lesion is a generalized maculopapular erythematous rash with itching. Any part of the body may be involved. In severe cases the skin is very rough to the touch, feeling somewhat like sandpaper. Pruritus is usually mild but may be extreme, so that the patient cannot rest until it is controlled. Often, but not always, there is an associated eosinophilia. The pruritus responds promptly to treatment with antihistaminic drugs; the rash usually does not. This type of eruption is usually self limited; it occurs typically at the end of the first week of treatment, lasts for from five to ten days and then spontaneously clears. In severe cases the eruption may last considerably longer. There is no reason to discontinue treatment. Six such cases occurred among 55 patients treated with 2 Gm. daily, an incidence of 11 per cent; 1 among 16 patients treated with 1 Gm. daily, an incidence of 6 per cent, and 2 among 66 persons treated with 0.5 Gm. daily, an incidence of 3 per cent.

Urticaria is rarer and may occur at any time after the first two weeks of treatment. Both the urticaria and the associated itching can be controlled by the administration of antihistaminic drugs for a brief period. However, the eruption often recurs as long as administration of the drug is continued. In one instance extensive urticaria made its appearance after two weeks of treatment and continued until tripelennamine hydrochloride (pyribenzamine hydrochloride®) was given. Treatment with tripelennamine hydrochloride was continued for the remainder of the course of streptomycin treatment and for one week more, with almost complete relief of symptoms. When treatment with tripelennamine hydrochloride was stopped, however, urticarial wheals recurred;

6. Rauchwerger, S. M.; Erskine, F. A., and Nalls, W. L.: Streptomycin Sensitivity: Development of Sensitivity in Nursing Personnel Through Contact During Administration of the Drug to Patients, J. A. M. A. **136**:614-615 (Feb. 28) 1948.

7. Dunner, E.: Personal communication to the authors.

a streptomycin patch test was positive, and no other hypersensitivity was demonstrated. Urticaria recurred at longer intervals, until finally, six weeks after the cessation of streptomycin therapy, the wheals disappeared permanently. The occurrence of urticaria is no reason for the discontinuation of streptomycin therapy.

Exfoliative dermatitis is a rare but serious complication of streptomycin therapy. Its occurrence is an indication for the immediate withdrawal of streptomycin. Only 1 case of this type was seen at this hospital. In this case a pruritic maculopapular eruption began after twenty-six days of treatment with streptomycin. This eruption persisted until the fortieth day, when exfoliation began; treatment with the drug was promptly stopped, and the skin slowly returned to normal. Three weeks later very small doses were tolerated well, but a single therapeutic dose (0.4 Gm.) caused an immediate intensely itching maculopapular eruption to appear all over the patient's body. Pruritus was most pronounced on the chest and upper extremities. Treatment with the drug was at once stopped. Several days later, the skin all over the body began to shed fine scales, while large areas of skin sloughed from the hands and feet. Each eruption was accompanied by eosinophilia, with a count of from 15 to 20 per cent; neither the itching nor the scaling was benefited by treatment with antihistaminic drugs. In most cases of exfoliative dermatitis reported by others, no previous benign rash existed.

In 2 instances the lips became dry and chapped, with fissuring and considerable soreness. In both cases the patients were receiving 2 Gm. of streptomycin daily; neither had eosinophilia, and neither was benefited by treatment with antihistaminic drugs. In both cases a degree of relief could be obtained by the use of bland ointments. This complication does not require the cessation of streptomycin therapy.

In 1 case the tongue became swollen, red and painful, with superficial ulceration covered with a yellowish membrane. This patient also was receiving 2 Gm. of streptomycin daily. There was moderate discomfort, but it was possible to continue treatment.

Three cases of dermatitis venenata were seen in nurses who had used streptomycin regularly over a long period of time. One case arose after six weeks of exposure, and the others, after three months. No cases were seen in personnel with limited exposure to streptomycin. In all these 3 cases reactions to patch testing were positive. In 2 cases the patch test was accompanied with a flare-up of the entire lesion, which exacerbation subsided in two or three days. In all cases the lesions subsided when contact with the drug was stopped—in 1 instance by the nurse's being moved to a ward where the drug was not used, and in the others by the wearing of rubber gloves. The lesions themselves were quite different in the 3 cases. One nurse had an itching vesicular

lesion involving the hands and forearms, worse in the interdigital spaces, and an itching maculopapular lesion involving the circumorbital regions, accompanied with a mild conjunctivitis. A second nurse had an intensely pruritic lesion involving all exposed surfaces. It was papular, and there were numerous excoriations on the forearms. This lesion was definitely aggravated by exposure to sunlight. Two exacerbations were produced by the investigators—one by a patch test and the other by twenty minutes' exposure to sunlight. The dermatitis cleared in a few weeks, on the patient's avoidance of contact with streptomycin; and at the time of writing, three months after contact with streptomycin was stopped, exposure to sunlight produced no eruption. The third patient had a macular eruption on the inner aspects of both forearms and large, itching urticarial patches on the trunk, as well as edema of both upper eyelids. These lesions were relieved by treatment with the antihistaminic drugs, cleared when contact with streptomycin ceased and were aggravated by a patch test.

SUMMARY AND CONCLUSIONS

Patients receiving streptomycin may acquire a toxic eruption of the skin or mucous membranes. There are several varieties: a maculopapular erythematous rash, pruritic and self limited; urticaria; exfoliative dermatitis, and stomatitis.

These reactions are rare when the daily dose of streptomycin is 1 Gm. or less.

Exfoliative dermatitis is the only cutaneous eruption which requires cessation of streptomycin therapy.

Dermatitis venenata is not uncommon in personnel handling streptomycin regularly over long periods of time. It can be avoided by frequent changes in the nursing personnel who come in contact with streptomycin or by having these nurses wear rubber gloves.

Veterans Administration Hospital.

KVEIM REACTION IN SARCOIDOSIS

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CONSIDERABLE interest has recently been aroused by Kveim's report [1] of the production of an unusual cutaneous reaction in patients with sarcoidosis by the intracutaneous injection of heated saline suspensions of tissue obtained from persons with active disease. Kveim found that after the transient inflammatory response caused by the trauma of such an injection had subsided, a small, indurated papule developed at the test site within a variable period of time. This delayed papular reaction was distinctive in that it often required weeks to attain its maximum size and usually remained visible for many months thereafter. Microscopic examination of tissue from sites of such reactions showed a histologic structure essentially the same as that of the lesions of the natural disease. Since control injections of Frei antigen and old tuberculin injected simultaneously with the suspensions of tissue into the same patients produced no comparable response, and, since the sarcoid material yielded negative results when injected intracutaneously into normal persons or persons with syphilis or lupus vulgaris, Kveim concluded that the cutaneous reaction was specific for sarcoidosis. He also postulated that the cutaneous response was based on an allergic mechanism, although no experimental support for that contention was presented.

Several years prior to the publication of these results, Williams and Nickerson [2] described a cutaneous reaction in sarcoidosis which, in retrospect, appears similar in some details to that reported by Kveim. These investigators, using an antigen of sarcoid tissue prepared in a manner nearly identical with that subsequently employed by Kveim, produced cutaneous reactions by intracutaneous injection in 4 cases of

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1. Kveim, A.: Preliminary Report on New and Specific Cutaneous Reaction in Boeck's Sarcoid, Nord. med. **9**:169-172, 1941.

2. Williams, R. H., and Nickerson, D. A.: Skin Reactions in Sarcoid, Proc. Soc. Exper. Biol. & Med. **33**:403-405, 1935.

sarcoidosis. The reactions, however, were described as transient, since none of the experimentally induced papules remained palpable for more than eight days. No mention was made of a delayed response after the initial inflammatory reaction had worn off, or of any unusual persistence of the experimental lesions—features which are characteristic of the typical Kveim reaction.

After the presentation of Kveim's results, other reports appeared which tended to confirm and extend the initial findings.[3] These studies indicated that a positive Kveim reaction occurred with a high degree of frequency in patients with sarcoidosis, even when there was no evidence of cutaneous involvement. It was suggested, therefore, that the Kveim test might be of considerable value in the diagnosis of the disease, particularly in cases of visceral lesions without extension to the superficial tissues. For a number of reasons, however, this possibility has not been realized, and the reaction has remained more a clinical curiosity than a test of diagnostic value.

So far as the specificity of the Kveim reaction is concerned, the published data seem to indicate that the cutaneous response is generally limited to patients with sarcoidosis and that positive results in other conditions are uncommon.[3e] In exceptional instances, however, a characteristic Kveim response has been observed in certain forms of tuberculosis of the skin, and, with some antigen preparations, positive reactions have been known to occur occasionally in normal persons.[3c,d] The latter fact emphasizes the need for testing the specificity of each lot of Kveim antigen on normal controls before using it in a clinical test. Even with this precaution the specificity of a given antigen may be difficult to assess, because, like the true positive reaction, a false positive response may require many weeks for its evolution. But, as a general rule, most Kveim antigens give positive results only in sarcoidosis and the test is regularly negative in such diseases as syphilis, leprosy, Hodgkin's disease, granuloma annulare, venereal lymphogranuloma, carcinomatosis and tuberculosis.[4]

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3. (*a*) Danbolt, N.: On Kveim's Reaction in Boeck's Sarcoid, Acta med. Scandinav. **114**:143-160, 1943. (*b*) Putkonen, T.: Ueber die Intrakutanreaktion von Kveim (KvR) bei Lymphogranulomatosis benigna und über das Bild dieser Krankheit im Lichte der Reaktionsergebnisse, Acta dermat.-venereol. (supp. 10) **23**:1-194, 1943. (*c*) Lomholt, S.: Beitrag zur Kveimreaktion bei Lymphogranulomatosis benigna, ibid. **24**:447-456, 1944. (*d*) Putkonen, T.: Ueber die Kveimreaktion bei Lymphogranulomatosis benigna, ibid. (no. 5) **25**:393-410, 1945. (*e*) Danholt, N., and Nilssen, R. W.: Investigations on the Course of Kveim's Reaction and Its Clinical Value, ibid. (no. 6) **25**:489-502, 1945.

4. (*a*) Putkonen.[3b] (*b*) Nelson, C. T.: Observations on the Kveim Reaction in Sarcoidosis of the American Negro, J. Invest. Dermat. **10**:15-26, 1948.

In another sense, however, there is considerable evidence that the Kveim reaction, rather than being a specific phenomenon, may be only a general cutaneous response on the part of persons with sarcoidosis to a number of different substances. For example, it has been shown that a reaction similar to that described by Kveim may sometimes be observed in cases of sarcoidosis after the intracutaneous injection of saline suspensions of leukemic human lymph nodes [3d] or killed tubercle bacilli.[5] More recently, it has been observed that patients who exhibit a positive cutaneous reaction to the injection of Kveim antigen prepared from sarcoid material may also give a typical Kveim response to the intracutaneous administration of suspensions of normal human spleen pulp.[4b] In these cases, biopsy specimens obtained from the site of injection of human spleen pulp after a period of several months often showed a histologic picture similar to that of a spontaneous sarcoid and fairly comparable to that induced by injections of Kveim antigen derived from sarcoid tissue. Thus, although the specificity of the Kveim reaction is such that the cutaneous response is usually limited to patients with sarcoidosis, the fact that such persons often react in an identical fashion to the intracutaneous administration of normal human spleen tissue, and sometimes of leukemic lymph nodes and tubercle bacilli, strongly suggests that the response does not depend on any specificity inherent in the sarcoid tissue used in the preparation of the antigen. Instead, such evidence indicates that the Kveim reaction as seen in patients with sarcoidosis may be only an unusual isomorphic response to one or more chemical complexes, present in certain human tissues and in other substances.

During the two years previous to this report, an opportunity to study the characteristics and possible clinical significance of the Kveim phenomenon was afforded by the presence of a group of 24 persons with proved sarcoidosis. These patients provided further data on certain features of the reaction; the intent of this report is to summarize the results of this experience to the time of writing.

MATERIALS AND METHODS

The cases of sarcoidosis included in this study were chosen at random from those of outpatients and patients admitted to the hospital with this disease. Twenty-one patients were Negroes and 3 were white. In most instances the chief manifestations were dermatologic, but in some the presenting symptoms were predominantly those of generalized sarcoidosis. Nevertheless, all but 4 of the

5. (*a*) Lemming, R.: Development of Boeck's Sarcoid at the Place on the Skin Where a BCG Vaccination Had Been Made in a Case of Schaumann's Disease, Acta med. Scandinav. **110**:151-160, 1942. (*b*) Warfvinge, L. E.: Boeck's Sarcoid Experimentally Produced by Virulent, Human Tubercle Bacilli in a Case of Schaumann's Disease, ibid. **114**:259-270, 1943.

patients exhibited cutaneous involvement at some time during the course of illness. The diagnosis of sarcoidosis in each case was established by microscopic examination of the affected tissue; supplementary confirmation of the diagnosis was obtained by repeated physical examinations, roentgenologic surveys and blood chemical studies. Tuberculosis was ruled out by microscopic examination and by cultural studies or inoculation of animals with biopsy specimens.

At intervals during the period of observation, efforts were made to estimate the activity of the disease in each patient. Sarcoidosis was arbitrarily classified as active when new lesions of the skin, mucous membranes or bones developed, or when there was evidence of progression or persistence of ocular symptoms, hilar adenopathy, infiltration of the parenchyma of the lungs or superficial glandular enlargement. All patients in the series were tested intracutaneously with 0.1 cc. of various dilutions of old tuberculin U. S. P., as well as with Kveim antigens and suspensions of normal human spleen in amounts of 0.15 cc.

Four Kveim antigens were used during the course of the study. Each was a 10 per cent suspension of microscopically proved sarcoid tissue in isotonic sodium chloride solution U. S. P. The suspensions were prepared by the method described by Nelson [4b] and were sterilized by heating in a water bath at 56 C. for two hours on each of two successive days. Two of the antigens were made

TABLE 1.—*Results of the Kveim Test in Twenty-Four Cases of Sarcoidosis*

State of Disease	Number of Cases	Number of Positive Reactions
Active	15	11
Inactive	9	0
Totals	24	11

from lymph nodes and two from skin. The donors were adult Negro patients in the active stages of the disease. For testing, 0.15 cc. of the antigen was injected intracutaneously through a 22 gage needle into the flexor surface of the forearm. The reaction was recorded as positive when a papule occurred at the injection site and remained palpable for at least sixty days from the date of its appearance. All persons for whom data are included in the present report were observed at one week to two week intervals for the first ninety days, and more irregularly thereafter, for a minimum period of twelve months. Each patient was tested with at least two Kveim antigens before final results were recorded. Some received injections of three or four different antigens; the amount of material available did not permit the administration of all four preparations to each patient. Whereas the antigens prepared from cutaneous lesions were satisfactory, those made from lymph nodes seemed superior. The latter yielded more homogeneous suspensions and, in general, seemed to produce more uniform reactions with less early inflammation than those made from skin.

At the time the Kveim test was administered, each patient also was inoculated intracutaneously with two heated 10 per cent suspensions of normal human spleen tissue in isotonic sodium chloride solution U. S. P. The spleen tissue was obtained at autopsy from the bodies of 2 white male patients who had died of cardiovascular disease. They had had no obvious infections and had shown no evidence of sarcoidosis. The suspensions of spleen tissue were prepared in the same manner as the Kveim antigen, and the criteria for determining the results of the inoculations were the same as those for the Kveim test.

The sarcoid antigens and suspensions of normal human spleen tissue employed in this study did not produce the characteristic delayed papular reaction when injected intracutaneously into normal persons, or into patients with diseases other than sarcoidosis. A certain amount of early inflammation occurred at the injection sites in all persons after the administration of these substances, but in the sarcoid-free controls this reaction was evanescent and disappeared within two or three weeks. Subsequent investigations, using material from a number of different

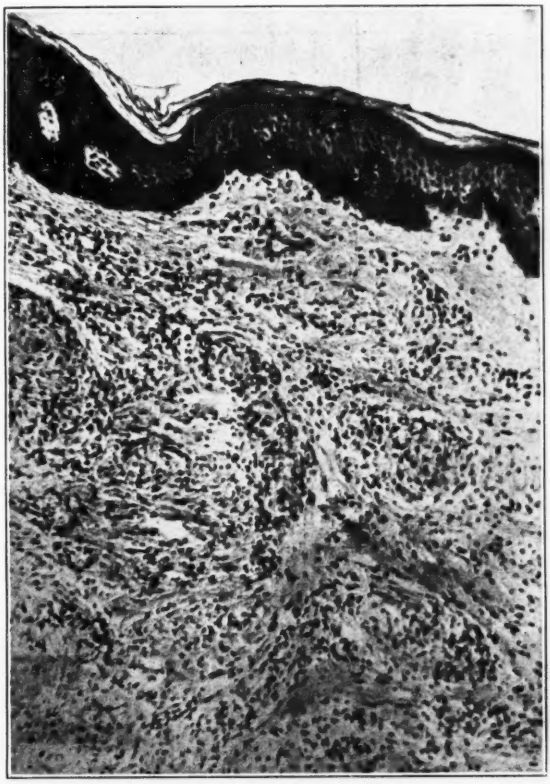

Fig. 1.—Sarcoid-like response ten months after the intracutaneous injection of Kveim antigen. The cells infiltrating the lesion are epithelioid cells and lymphocytes. Giant cells were rare. Hematoxylin and eosin stain; × 100.

normal human spleens, have shown that some suspensions of spleen tissue may lose their specificity after several months of storage and produce persistent papular lesions in nearly all persons after intracutaneous injection.[6] The reason for this phenomenon is not known, but it again emphasizes the need for frequent evaluation of the specificity of such products before their use in tests of this sort.

6. Nelson, C. T.: Unpublished data.

It is also not clear whether all suspensions of material from normal human spleens are capable of producing the Kveim response in patients with sarcoidosis. As is true of Kveim antigens prepared from sarcoid tissue, suspensions of normal human spleen apparently may also vary considerably in their capacity for inducing the sarcoid response.

RESULTS

The data in table 1 show that the Kveim reaction was positive in 11 of the 15 patients with active sarcoidosis. In none of the 9 patients with healed or

Fig. 2.—Extensive production of sarcoid-like tissue seven months after the intracutaneous administration of a suspension of normal human spleen. Note naked tuberculoid structure, with occasional giant cells of the Langhans type. Hematoxylin and eosin stain; × 100.

inactive sarcoidosis was a positive reaction obtained. These results indicate that negative Kveim reactions may be expected in a significant number of patients even with the clinically active stages of sarcoidosis, and that, consequently, the test can be of only limited diagnostic value. However, it is possible that the reaction may be of some help in anticipating the course of the disease, since

reactions in the patients in whom the disease was in remission were all negative. Further evidence of the value of the test in prognosis is the result noted in 4 persons with active sarcoidosis in whom the disease entered a phase of clinical remission during the period of study. In 2 of these patients, reactions to repeated Kveim tests were negative from the beginning of observation. After six months and seven months, respectively, the clinical signs of sarcoidosis subsided rather rapidly, and both patients subsequently remained asymptomatic. In the 2 other patients clinical remission occurred ten months and thirteen months, respectively, after the start of observation. In both instances, the Kveim reaction was originally positive, but the experimental lesions began to involute as the patients approached the stage of clinical improvement. Thereafter, reactions to repeated Kveim tests in these patients were negative, despite the fact that the reactions had previously been positive.

TABLE 2.—*Various Clinical Manifestations and Results of the Kveim and Other Intracutaneous Tests in Fifteen Patients with Active Sarcoidosis*

				Sites of Lesions							Results of Intracutaneous Tests					
													Old Tuberculin U.S.P.			
Case Number	Age, Years	Sex	Months Since Onset of Disease	Skin	Hilar Lymph Nodes and/or Lung	Superficial Lymph Nodes	Salivary or Lacrimal Glands	Bone	Eye	Other*	Kveim†	Spleen Suspensions‡	1 mg.	0.1 mg.	0.01 mg.	0.001 mg.
1	34	F	99	0	±	+	+	0	+	+	+	+	0	0	0	0
2	44	F	82	+	+	±	+	0	+	+	+	+	0	0	..	..
3	41	F	56	+	±	+	0	0	0	+	+	+	±	0	0	..
4	34	M	63	+	±	+	0	0	0	+	+	+	0	0	0	..
5	50	M	73	+	+	+	0	0	0	±	+	+	+	0	0	0
6	43	F	24	+	+	±	0	0	0	0	+	+	±	0	0	..
7	32	F	34	+	+	0	0	0	0	+	+	+	0	0	0	..
8	40	F	37	+	+	±	0	0	0	0	+	+	..	+	0	0
9	40	F	22	+	0	0	0	0	0	0	+	+	0	0	0	0
10	32	M	37	+	+	+	0	+	0	0	+	+	0	0	0	..
11	36	F	18	+	+	0	+	0	0	0	+	+	+	±	0	0
12	40	F	25	0	0	+	0	0	0	0	0	0	±	0	0	..
13	26	F	22	+	+	±	0	0	0	+	0	0	0	0	0	0
14	24	F	35	+	0	+	0	0	0	+	0	0	0	0	0	..
15	24	F	13	+	0	+	+	0	0	+	0	0	0	0	0	..

+ = Present or positive; ± = equivocal; 0 = absent or negative.
* Case 1, coincidental weakness of facial nerve; case 2, tonsils; cases 3, 4 and 7, mucous membrane; cases 5, 13 and 14, palpable spleen; case 15, palpable liver.
† Results obtained with two or more antigens.
‡ Results obtained with two suspensions of human spleen.

Thus, in this group of patients, 9 persons in whom sarcoidosis was already inactive gave negative Kveim reactions; 4 others, who were about to show clinical remission, showed negative reactions either at that point or as the disease began to subside. These data suggest that the test, although it may not be much help in the diagnosis of sarcoidosis, may be of some use in judging the prognosis in a case at hand. If reactions to successive Kveim tests remain persistently positive in a case of active disease, the probability is that clinical improvement is still some time away.

It is of interest that the pateints who showed a positive cutaneous reaction to the injection of sarcoid material without exception also presented a typical Kveim response to the intracutaneous injection of normal human spleen tissue. Biopsy specimens taken from the sites of both tests after a period of six to ten months showed a histologic picture comparable to that of a spontaneous sarcoid (figs. 1 and 2). Attempts to correlate the development of these characteristic

reactions to cutaneous tests with the various clinical manifestations of sarcoidosis, or with the degree of sensitivity exhibited by these patients to old tuberculin U.S.P., were unsuccessful. While the number of cases in the present series is too small to

TABLE 3.—*Sites of Previous Lesions and Results of Kveim and Other Intracutaneous Tests in Nine Cases of Healed or Inactive Sarcoidosis*

				Sites of Lesions During Active Phases of Disease							Results of Intracutaneous Tests					
													Old Tuberculin U.S.P.			
Case Number	Age, Years	Sex	Months of Remission	Skin	Hilar Lymph Nodes and/or Lung	Superficial Lymph Nodes	Salivary or Lacrimal Glands	Bone	Eye	Other*	Kveim†	Spleen Suspensions‡	1 mg.	0.1 mg.	0.01 mg.	0.001 mg.
16	37	F	26	+	+	+	0	0	0	+	0	0	..	+	0	0
17	26	F	17	+	+	0	0	0	0	0	0	0	..	+	+	0
18	42	F	28	+	±	0	0	0	0	0	0	0	+	±	0	0
19	54	F	53	0	+	+	+	±	+	+	0	0	..	+	0	0
20	34	F	29	0	+	+	0	0	0	+	0	0	..	+	0	0
21	40	F	104	+	+	0	0	+	0	+	0	0	..	+	+	+
22	58	F	46	+	+	+	0	+	0	+	0	0	..	+	0	0
23	39	F	61	+	0	+	0	0	0	0	0	0	..	+	0	..
24	34	F	40	+	+	0	±	0	+	0	0	0	..	+	0	0

+ = Present or positive; ± = equivocal; 0 = absent or negative.
* Cases 16, 21 and 22, mucous membrane; case 19, palpable liver; case 20, palpable liver and spleen.
† Results obtained with two or more antigens.
‡ Results obtained with two suspensions of human spleen.

TABLE 4.—*Serum Values in Fifteen Cases of Active and Nine Cases of Inactive Sarcoidosis*

	Laboratory Observations							
Classification and Case Number	Total Proteins, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Alkaline Phosphatase, Bodansky Units per 100 Cc.	Cephalin Flocculation (48 Hr.)	Calcium, Mg. per 100 Cc.	Inorganic, Phosphorus, Mg. per 100 Cc.	Total Cholesterol, Mg. per 100 Cc.
Active sarcoidosis				Kveim Positive				
1	8.2	3.7	4.5	7.0	0	8.8	4.1	175
2	7.3	4.5	2.8	1.8	++	....	4.4	192
3	7.4	4.7	2.7	5.9	±	9.3	...	247
4	8.1	4.4	3.8	10.1	0	10.2	3.1	149
5	7.4	3.9	3.5	5.9	++	....	3.4	250
6	7.8	3.9	3.9	3.3	0	10.0	...	265
7	7.5	4.2	3.3	2.5	0	9.6	3.2	246
8	7.5	4.9	2.6	1.9	0	9.9	...	...
9	6.9	4.2	2.7	1.6	....	10.3	4.1	208
10	8.4	4.2	4.2	5.8	++	11.0	4.3	179
11	6.8	4.2	2.6	3.2	++	10.4	3.7	204
				Kveim Negative				
12	7.3	3.8	3.5	2.8	±	10.1	3.8	...
13	9.4	4.1	5.3	6.4	++	10.7	...	260
14	8.4	4.1	4.3	3.6	+++	9.8	3.8	222
15	7.1	3.5	3.6	2.5	0	11.0	4.6	...
Inactive sarcoidosis				Kveim Negative				
16	8.0	4.5	3.5	14.4	0	....	3.6	234
17	7.2	4.6	2.6	3.3	....	10.8	3.2	...
18	7.7	4.2	3.5	4.2	0	10.3	3.7	165
19	7.3	5.1	2.2	5.0	+	10.6	4.8	...
20	8.3	4.7	3.6	6.9	++	9.7	3.1	199
21	9.0	3.7	5.3	3.3	0	11.8	...	167
22	8.1	5.0	3.1	2.0	....	10.8	3.9	321
23	6.8	3.3	3.5	1.9	+	....	4.0	...
24	7.7	4.7	3.0	3.5	0	10.0	3.9	142

permit definite conclusions, the data presented in tables 2 and 3 do not suggest that the capacity for characteristic cutaneous reactions to Kveim antigens and suspensions of normal human spleen is associated with any particular type or degree of sarcoidosis. As might have been expected, the patients with the inac-

tive stage of the disease showed a generally higher level of reactivity to old tuberculin than did those with active sarcoidosis. Although slight variations in sensitivity to tuberculin occurred in persons with active sarcoidosis, the variations seemed to bear no obvious relation to the ability or inability of the persons to react to suspensions of human spleen and sarcoid tissue.

A number of laboratory studies were also undertaken in the cases of this series to learn whether the presence of a cutaneous response to injections of sarcoid material and human spleen tissue might be related in some way to variations in the values for certain constituents of the blood. The results of these observations are summarized in table 4. The values are those obtained at the time the cutaneous tests were administered. It is evident from these data that there was no clearcut relation between the various blood values in sarcoidosis and the cutaneous reaction to Kveim antigen and suspensions of human spleen.

COMMENT

It seems apparent from the studies presented in this report and elsewhere [7] that many persons with clinical sarcoidosis respond in a typical manner to the intracutaneous administration of various organic materials. After such injections, delayed papular reactions, having a histologic structure comparable to that of a spontaneous sarcoid, often develop at the test sites. Responses of this sort may be produced with some regularity with injections of heated saline suspensions of sarcoid tissue, normal human spleen pulp, leukemic lymph nodes and tubercle bacilli. On the other hand, intracutaneous injections of saline suspensions of calcium sulfate, collodion particles, coagulated egg white, Pityrosporum ovale, defatted human skeletal muscle, normal human lymph nodes and oil-free soybean phosphatides do not result in such reactions.[4b]

It has been known for many years that lesions having the microscopic anatomy of typical sarcoids can sometimes be produced experimentally by the injection of certain oils, as well as lipid-containing extracts of various bacteria. Moreover, it is also well established that local histologic changes comparable to those seen in sarcoidosis may be found in such conditions as tuberculoid leprosy, syphilis, tuberculosis, leishmaniasis, brucellosis, chronic beryllium poisoning and certain fungous infections. These facts are only suggestive, but they lend some support to the viewpoint, shared by many investigators, that the tissue reactions in sarcoidosis are not in themselves specific but merely represent a general histologic response to a number of different agents. With this possibility in mind, it is perhaps understandable that certain persons with active sarcoidosis who seem to possess this general type of tissue reactivity to a considerable degree should respond in a similar fashion to the injection of several seemingly different substances.

7. Kveim.[1] Danbolt.[3a] Putkonen.[3b] Lomholt.[3c] Putkonen.[3d] Danbolt and Nilssen.[3e] Nelson.[4b] Lemming.[5a] Warfvinge.[5b]

The exact nature of the chemical complexes which are capable of artificially inducing these sarcoid-like tissue reactions has not been determined. There is evidence that some, at least, are relatively heat stable: It has been shown that Kveim antigens can withstand boiling for twenty minutes without loss of reactivity.[3d] Other preliminary studies suggest that the active principles in normal human spleen tissue are associated in some way with the lipid fractions.[6] But whatever the chemical nature of the agents responsible for the unusual tissue reactions in question may be, it is clear that the agents can produce sarcoid responses only when injected in grossly particulate form. Berkefeld filtrates of Kveim antigen or suspensions of normal human spleen do not induce the characteristic cutaneous reactions. Thus, the Kveim response and other similar phenomena observed in patients with sarcoidosis seem to depend not only on the chemical makeup of the materials injected but also on the size of the particles. Unless the particles of injected material can serve as localized depots of stimulation for relatively long periods of time, the typical cutaneous reactions will not ensue. Some investigators[8] have suggested that the Kveim response is an allergic phenomenon. If this is true it is difficult to explain the delayed appearance of the reaction, unless one postulates that a prolonged latent period is needed before the sensitized tissue can react with the immobilized aggregates of antigen. Evidence for this is lacking, however, and for the present it may be just as fruitful merely to regard the Kveim reaction as a general tissue response on the part of patients with sarcoidosis to a chemical foreign body.

Attempts to employ the Kveim reaction in the diagnosis of sarcoidosis have not been particularly successful. The antigens used thus far not only have been relatively crude and difficult to standardize but also have had the disadvantage of producing extremely persistent nodular lesions in positive reactors. Sometimes these lesions become necrotic and form disfiguring ulcers, which may require many months to heal.[3c, d] In addition, although false positive reactions are uncommon, a certain number of patients with active disease apparently do not respond to the test. Even when the reaction is positive, it may be so delayed in its evolution that it loses much of its practical diagnostic significance. On the other hand, there is some evidence that the test may be of occasional prognostic value in following the course of the disease, since in some instances the Kveim reaction has involuted completely at the time when the patient began to show evidence of clinical remission. Aside from this apparent association with the activity of the disease, the Kveim response does not seem to have any obvious relation to the type or degree of clinical involvement, or to the characteristic changes in certain blood values in patients with sarcoidosis.

8. Kveim.[1] Danbolt.[3a]

SUMMARY

1. In a study of the Kveim phenomenon in 24 cases of sarcoidosis the reaction was positive in 11 of 15 patients with active disease. In none of the 9 cases of healed or inactive sarcoidosis in the group was a positive Kveim response obtained.

2. All persons who showed a positive cutaneous reaction to the injection of Kveim antigen also showed a typical sarcoid-like response to the intracutaneous injection of suspensions of normal human spleen tissue.

3. The capacity for these characteristic cutaneous reactions did not seem to have any consistent relation to the type of clinical involvement, to the degree of sensitivity to tuberculin or to changes in the values for certain blood constituents observed in sarcoidosis.

4. Although the Kveim reaction is of little value in the diagnosis of sarcoidosis, there is some evidence that it may be of occasional prognostic use in following the course of the disease.

630 West One Hundred and Sixty-Eighth Street (32).

ABSTRACT OF DISCUSSION

DR. MAX MICHAEL, Chamblee, Ga.: This so-called Kveim reaction is indeed unique. The long latency for its development, sometimes as long as eighteen months before it becomes positive, would certainly remove it from the group of intracutaneous reactions such as the immediate anaphylactic reaction or the delayed tuberculin type reaction.

Dr. Nelson has wisely stressed the complete nonspecificity of the reaction. One should call to mind the number of cases in which sarcoid lesions have been reported after trauma. One cannot say that these patients have sarcoidosis, but rather that sarcoid lesions developed after trauma in which bits of silica or sand were apparently driven into the skin. This view would suggest that the Kveim reaction and the type of reaction which appears after trauma with silica represent the capacity of the patient to react to certain foreign, extraneous materials, as Dr. Nelson has emphasized.

It seems that the usefulness of the Kveim reaction will lie not in its diagnostic value and perhaps not so much in its prognostic value, but probably in its being just another tool with which we can study the pathogenesis of disease.

If one could find out exactly what brings about the Kveim reaction, and the chemical fractionation of the tissue responsible for it, then one could better understand the whole mechanism and pathogenesis of sarcoidosis.

I should like to ask Dr. Nelson two questions concerning results using the various fractions: First, is the histologic structure comparable to that seen with the sarcoid tissue? Secondly, does the reaction appear in a length of time shorter than that when the whole tissue extract is used?

DR. JOHN DALTON, Indianapolis: The workers at Indianapolis General Hospital have been pursuing studies on the Kveim reaction. I should like to report on our work because this presentation clarifies some of our confusing results. Dr. Morris Leider provided us with some Kveim antigen which he had received from Dr. Putkonen. The amount was small. We selected 6 patients with sar-

coidosis, clinically characteristic and histologically proved. Intracutaneous tests were made and the patients watched over a long period. However, no reaction developed at the injection site in any of the patients. Three of the patients had a regressing stage of the disease when they were tested. This would corroborate Dr. Nelson's finding of reduced positivity or complete negativity in similar cases when the active process was on the wane. However, he reported negative Kveim reactions when patients in active stages of the disease were tested with old antigens. This again may be a factor in our failure to obtain positive reactions, because the antigen which we used was at least six months old.

Furthermore, we prepared an antigen with tissue obtained from a patient whose condition was definitely improving. When the material was used in testing persons who manifested active sarcoid disease, the results were negative. I should like to ask Dr. Nelson if he has had a similar experience. I should like to say one additional thing regarding sarcoid-like tissue reactions in general. Lately I observed a patient who had been working beneath a fluorescent light when it fell and broke, lacerating the dorsum of her hand. Early healing progressed uneventfully, but, when closure was almost complete, several small papules developed about the edges of the injured site. Biopsy sections revealed beryllium particles; I regarded the particles as causative of the tissue reaction shown.

Dr. Bernard Appel, Lynn, Mass.: It is useful for Dr. Nelson to have revived this particular subject, especially because some contradictory statements have been made, particularly in regard to the specificity of the test. At the Boston City Hospital, in the dermatology department, this test has been performed since 1934, which, incidentally, was a long time before Kveim did his work. In Boston, Donald A. Nickerson and R. H. Williams, back in 1932, conceived the idea that sarcoidosis or sarcoid-like lesions might produce a specific virus type reaction similar to that in venereal lymphogranuloma. They removed sections from lesions, ground them up, made a sterile suspension, performed tests and reported their observations.[2]

The question is: What about the specificity of this test? It appears to me that it is specific. The mere fact that a patient with sarcoidosis or a patient with sarcoid-like lesions also reacts to an injection of tuberculin or spleen tissue does not necessarily mean that this particular test is nonspecific. After hearing this excellent presentation, my impression is that a pretty good case has been made out for its specificity. I would not go any further than the author of the paper in proposing it as an absolute, iron-clad test, but I think pursuit of the subject should lead to still more knowledge. The corollary of the statement that patients whose disease is in remission do not exhibit the positive Kveim response is that periodic retesting of patients with active, progressive symptoms of the disease ought to give a fairly reasonable picture of the possibility of prognosis and of the development of the disease.

Another interesting phenomenon, which Kveim himself noted in his paper in 1941, was that the latent interval which elapsed between the inoculation and the development of the nodule grew progressively shorter and shorter as the disease progressed in its intensity. The implications of that observation should be studied further. I want to take this opportunity again to protest against eponymic nomenclature. I do not see what is gained by hitching a man's name onto a test like this. Let us instead call it an intradermal skin test for sarcoidosis; scientific progress is thus better served. Eponyms have only historical value and cater to vanity.

DR. MAURICE OPPENHEIM, Chicago: I wish to make only a short remark about the sarcoid reaction of the skin in general. About twenty-five years ago, I reported several cases of localized sarcoids or lipid reactions in sites where subcutaneous injections had been made with soluble and insoluble drugs, like suspensions of mercury or bismuth in oil. Later, Volk performed experiments in which he was able to produce sarcoids by subcutaneous injections of india ink. This shows, as Dr. Nelson and the other speakers pointed out, that the sarcoid reaction may be a specific reaction of the skin. This reaction should not be confused with the foreign body reaction, which is histologically different. In an excellent paper on sarcoidosis, which Dr. Michelson read a year ago in Atlantic City, he mentioned my data.

DR. CARL T. NELSON, New York: Dr. Michael's suggestion that the injection of silica-containing material may produce a sarcoid-like response, comparable to that induced by the Kveim antigen, is well taken. Tissue reactions to silica can mimic the Kveim reaction in almost every detail; that is why sand must not be used for grinding the tissue during the preparation of antigen suspensions of this sort.

A clarification of the mechanism of the Kveim response might be helpful in explaining the pathogenesis of naturally occurring sarcoid lesions. At present, little is known about the chemical makeup of the substances which can provoke the Kveim type of reaction. Recently, I have tried to isolate the active fractions which are known to be present in at least some normal spleens. I have not been successful thus far, but there is evidence that the active principles are linked with compounds of a lipid nature.

As Dr. Dalton has indicated, antigens prepared from different specimens of sarcoid tissue may vary greatly in their ability to produce the Kveim response. The period during which an antigen will retain its reactivity also seems subject to considerable variation. However, I am not in a position to comment on this point, since my woefully small supplies of antigen have always been used up in a few months.

The occurrence of localized sarcoid granulomas in persons who have cut themselves on broken fluorescent lamps coated with beryllium phosphor is very interesting. The histology of these traumatic lesions is similar to that in spontaneous sarcoids and to that in the cutaneous lesions of workers in whom pulmonary granulomatosis has developed after exposure to beryllium.

In reply to Dr. Appel, let me emphasize that the Kveim reaction is specific in the sense that it is usually limited to persons with active sarcoidosis. Positive responses in other diseases are uncommon. On the other hand, the reaction is nonspecific in the sense that a similar response may be elicited in patients with sarcoid after the administration of substances other than sarcoid tissue. In other words, the Kveim response does not depend on any specificity inherent in the tissue used in the antigen. Sometimes suspensions of tubercle bacilli or normal spleen tissue will do as well.

In my experience, the performance of repeated Kveim tests over a period of months in cases of active sarcoidosis has not shortened the time required for a positive reaction. This might be taken as evidence against the theory that the reaction depends on an allergic mechanism. If it did, one might expect acceleration of the response under these circumstances.

Dr. Oppenheim may be correct in considering the Kveim reaction to be primarily a foreign body response. Apparently he has been able to produce sarcoid-like lesions with many more substances than I.

DISSEMINATED AND CIRCUMSCRIBED NEURODERMATITIS TREATED WITH PHENINDAMINE (THEPHORIN®)

WILFRED E. WOOLDRIDGE, M.D.*
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AND
HERBERT L. JOSEPH, M.D.
Resident in Dermatology
ST. LOUIS

IN 1910 Dale and Laidlaw [1] advanced the hypothesis that histamine or histamine-like bodies were the chemical compounds responsible for the phenomena of anaphylaxis. Since that time numerous investigators have produced evidence which seems to confirm that original idea, and the hypothesis has been extended to explain all or most of the phenomena associated with allergy in the broadest sense.

Diphenhydramine hydrochloride (benadryl hydrochloride®) and tripelennamine hydrochloride (pyribenzamine hydrochloride®) were the first drugs available in this country which seemed to play the role of "antihistaminic" agents, although they were preceded in Europe by numerous other preparations. Chemists have been and are still trying to find an ideal drug which (1) will have little or no side effects and (2) will produce better effects through penetration of the skin.

However strong the evidence may seem, histamine has never been proved entirely responsible for all the allergic manifestations attributed to it. Notable has been the failure of histaminase, an enzyme shown to be capable of inactivating histamine but disappointing when applied clinically. Also must be considered the failure of the "antihistaminic" drugs to inactivate histamine in vitro and the lack of any but circumstantial evidence that such inactivation occurs in vivo. At any rate, histamine is apparently not initially involved in the process which leads to anaphylaxis or allergic manifestations, for there first occurs an antigen-antibody reaction resulting in cell injury. At that point histamine first enters the picture, either being a direct product of the antigen-antibody reaction

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Studies, observations and reports from the Department of Dermatology of the Barnard Free Skin and Cancer Hospital and Washington University School of Medicine, service of Dr. Richard S. Weiss.

1. Dale, H. H., and Laidlaw, P. R.: The Physiological Action of Beta-Iminazolylethylamine, J. Physiol. **41**:318-344, 1911.

or being released by the injured cells. It is evident, therefore, that "antihistaminic" drugs probably play no part in preventing the anaphylactic or allergic reaction but rather prevent, in a still unrecognized way, the clinical manifestations which are recognized.

If these theories are correct, the "antihistaminic" drugs are at once relegated to the position of stopgaps in therapy, for they do not prevent the allergic reaction but only modify it. This contention is borne out by the many examples in which hay fever or urticaria, for example, is controlled for long periods only to have the patient suffer a relapse when use of the "antihistaminic" drugs is discontinued. However, the success with which these drugs are employed has resulted in a discouraging tendency for all attempts at discovery of offending agents to cease.

It is now known that the "antihistaminic" drugs may accomplish some of their actions without histamine being involved at all. That this statement is clearly true will be subsequently indicated by our studies and is already shown with regard to the anesthetic action of these drugs as related by Friedlander and Feinberg.[2] Also, the sedative action of these drugs is well known and seems to be entirely separate from their properties as histamine antagonists.

This paper reports the use of a new drug, phenindamine (thephorin®), which must be included in the group of drugs used in the symptomatic relief of allergic disease.[3]

CHEMISTRY

Phenindamine not only is a different antihistaminic agent but belongs to an entirely new and heretofore unknown series of compounds. It is a polycyclic amine, the empiric formula of which is $C_{19}H_{19}N$ (2-methyl-9-phenyl-2, 3, 4, 9-tetrahydro-1-pyridindene). Of this series of compounds only phenindamine has shown significant antihistaminic activity. The structural formulas of two others of this series, differing from phenindamine only by the position of their double bonds, are shown in figure 1 and are considered briefly in this paper. The structural formulas for diphenhydramine hydrochloride (beta-dimethylaminoethyl benzohydryl ether hydrochloride) and for tripelennamine hydrochloride (N, N - dimethyl - N′- benzyl - N′- [α - pyridyl] ethylenediamine hydrochloride) are shown for comparison. The similarity between diphenhydramine hydrochloride and tripelennamine hydrochloride may be seen,

2. Friedlander, S., and Feinberg, S.: Histamine Antagonists: III. The Effect of Oral and Local Use of Beta-Dimethyl-Amino-Ethyl Benzhydryl Ether Hydrochloride on the Whealing Due to Histamine, Antigen-Antibody Reactions, and Other Whealing Mechanisms: Therapeutic Results in Allergic Manifestations, J. Allergy **17**:129-141 (May) 1946.

3. All materials for this study were supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

and these drugs, together with the remaining commercial antihistaminic compounds, except for phenindamine, are derivatives of the older Forneau compounds. As indicated previously, phenindamine, which to date is chemically unique and distinct from the others now available, is not.

The phenindamine base has a melting point of 90 to 91 C. The salts of the base which are employed clinically melt at considerably higher temperatures. At room temperature the tartrate salt is soluble, up to 3 per cent, in water. A 2 per cent aqueous solution has a *p*H of 5.

PHARMACOLOGY

Toxicity studies have revealed that phenindamine shows approximately the same degree of toxicity to animals as does diphenhydramine

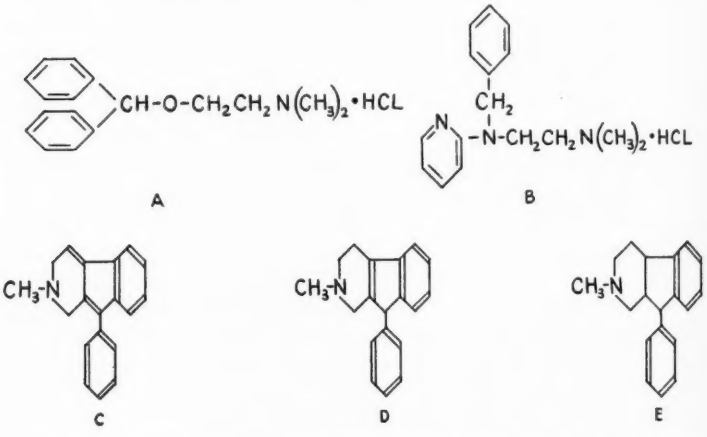

Fig. 1.—Structural formulas for diphenhydramine hydrochloride (*A*), tripelennamine hydrochloride (*B*), Nu-1326 (*C*), Nu-1504, or phenindamine (*D*) and Nu-1525 (*E*).

hydrochloride but considerably less than does tripelennamine hydrochloride. Guinea pig protection experiments against a histamine spray showed a more favorable milligram per kilogram protection with phenindamine than with diphenhydramine hydrochloride but less with phenindamine than with tripelennamine hydrochloride. In man it was shown that the size of histamine wheals was moderately reduced when phenindamine was taken by mouth and also that the erythema was much less and itching completely absent in 5 of 6 subjects. Lehmann [4] showed

4. Lehmann, G.: Pharmacological Properties of a New Antihistaminic. 2-Methyl-9-Phenyl-2,3,4,9-Tetrahydro-1-Pyridindene (Thephorin) and Derivatives. J. Pharmacol. & Exper. Therap. **92**:249-259 (March) 1948.

that phenindamine is a potent local anesthetic and that it is longer acting, in equivalent concentrations, than procaine.

In addition to these effects, phenindamine has some properties which are the opposite of those of the more familiar antihistaminic drugs. It minimizes a histamine-induced vasodepression in cats, and it is necessary for one to administer ten to twenty times as much histamine intravenously to secure a fall in blood pressure following the administration of 1 mg. per kilogram of phenindamine as would be needed to secure a similar fall without phenindamine. Likewise, in man the principal symptomatic effects have been nervousness, sleeplessness and irritability rather than the more familiar hypnotic reactions which are customarily seen when other antihistaminic substances are employed.

CLINICAL STUDIES

Technic.—In this study we have employed phenindamine in a syrup containing 10 mg. per 4 cc., in tablets containing 25 mg. each and as a 5 per cent ointment, in a carbowax 1500® vehicle.

Two series of patients were treated. The first series was of persons with disseminated neurodermatitis (atopic eczema) and consisted of 23 treated and 7 control patients. The second series consisted of persons with circumscribed neurodermatitis (lichen chronicus simplex) and contained 14 treated and 3 control patients. In addition to these, 1 patient with disseminated neurodermatitis and another with circumscribed neurodermatitis were treated with the compounds Nu-1326 and Nu-1525. The essential data regarding the diseases of the patients treated with phenindamine and of the control patients appear in tables 1 and 2.

Of the patients with disseminated neurodermatitis, 9 of the treated group and 3 of the control group gave a family history of allergic disease, while no such history could be elicited in the rest. With 1 exception the entire group of patients with disseminated neurodermatitis were treated during the winter, and that portion of the study was terminated before warmer weather occurred and before any spontaneous clearing could be noted in other patients not included in this report. The exception was a control patient (S. D.), whose eruption had been present since birth and showed no seasonal variation.

Phenindamine was employed in the form of the hydrogen tartrate salt in the tablets and the syrup. The phosphate salt was used in the ointment. The compound Nu-1326 (2-methyl-9-phenyl-2,3-dihydro-1-pyridindene) was in the form of the hydrobromide salt, while Nu-1525 (2-methyl-9-phenyl-2,3,4,4a-9,9a-hexahydro-1-pyridindene) was used as the amine.

The doses employed by us were not as large as those used by Kesten and Sheard.[5] Our dose for adults was usually 25 mg., given three times daily, and it was never more than 100 mg. daily. The total daily dose for infants was 15 to 20 mg., and that for children, 30 to 40 mg.

Customarily, the ointment was applied three times daily and was gently massaged into the skin. It was applied to acute, weeping areas without hesitation. No other treatment was given to the patients during the time that phenindamine phosphate or the ointment base was used. All patients showing any signs of

5. Kesten, M. B., and Sheard, C.: Treatment of Allergic and Some Other Dermatoses with Thephorin, J. Invest. Dermat. **9**:65-66 (Aug.) 1947.

irritation during use of the ointment were given patch tests with the complete ointment and also with the ointment base.

Results of Treatment.—As will be seen from the data recorded in tables 1 and 2, the treatment of disseminated neurodermatitis met with more success than did the treatment of circumscribed neurodermatitis.

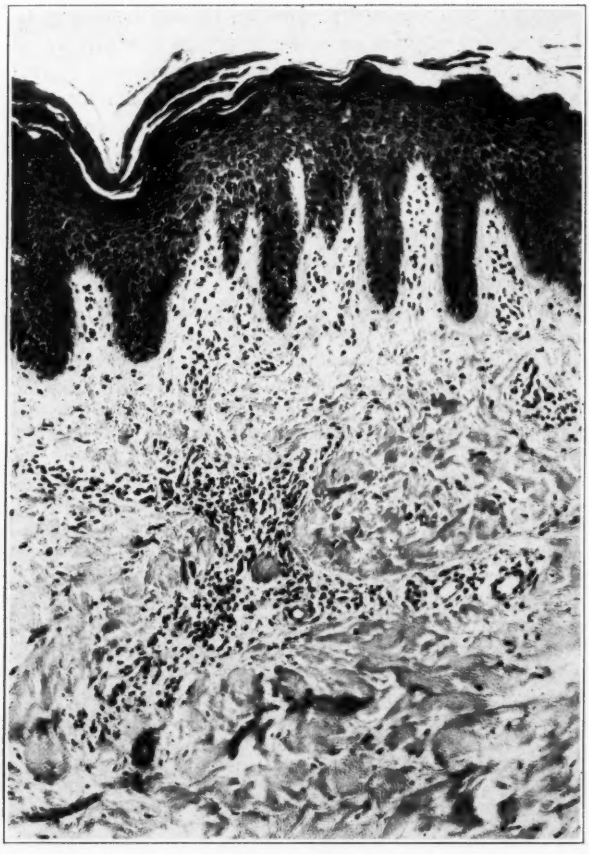

Fig. 2.—Photomicrograph of skin from the right antecubital space of patient (D. S.) with severe disseminated neurodermatitis, before treatment (× 115).

Disseminated Neurodermatitis.—It was encouraging to note that many of the patients with disseminated neurodermatitis insisted on the continuation of this treatment because it gave the only significant relief they had ever received from therapy other than roentgen rays. It will be noted from table 1 that only 2 of the 23 patients had complete

clearing of the eruption. The skin of those patients has remained clear to date. This result is in agreement with observations in other forms of therapy for this disease in that cure occurs so seldom that the clinician is content to have his patients comfortable, to bring them some degree of improvement and to expect no more. So far as we could tell, there was

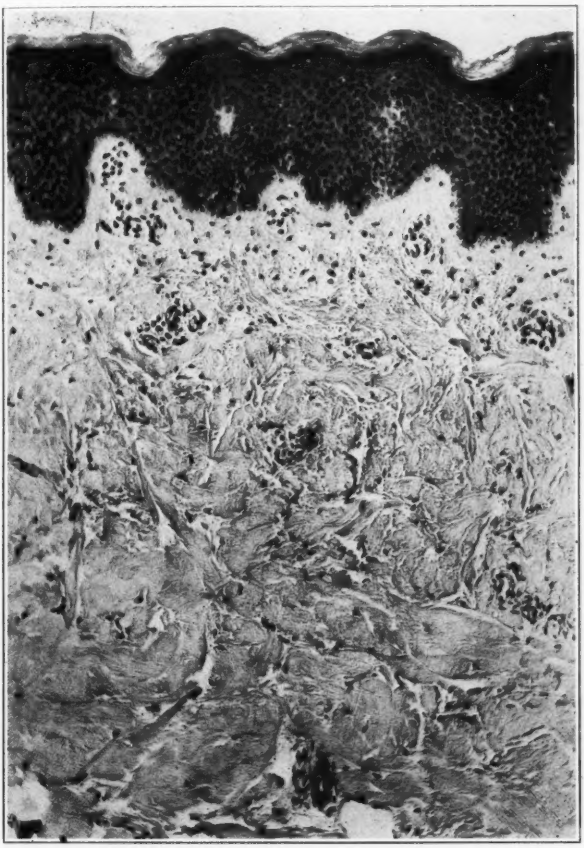

Fig. 3.—Photomicrograph of skin from an identically involved area of the right antecubital space of patient (D. S.), after two weeks of treatment with phenindamine (× 115). The progress toward a more nearly normal epidermis and the diminution of the edema, vascular dilatation and round cell infiltration in the cutis are clearly seen.

no difference between the response to treatment of the so-called "atopic" group, i. e., those with a positive family history, and that of those without

any such history. Likewise, we could not correlate the amount of improvement with the degree of involvement.

With most of our patients the relief of itching was dramatic after the first application of the ointment. Relief occurred within fifteen minutes and usually lasted two to three hours or longer. There was

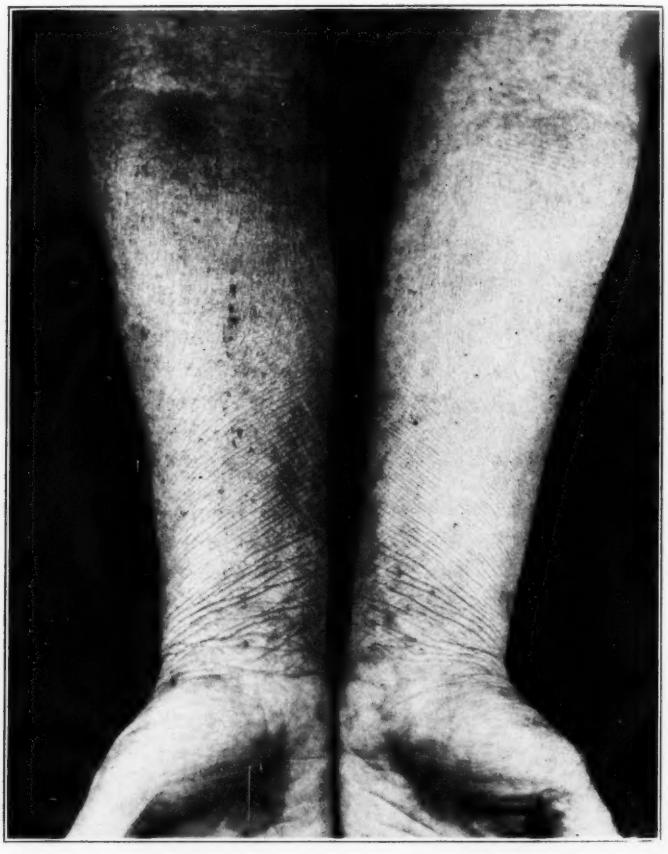

Fig. 4.—Photograph of forearms of control patient (J. R.) with severe, generalized disseminated neurodermatitis of many years' duration, taken after one week of local treatment with phenindamine phosphate ointment to the left arm and application of ointment base only to the right arm.

occasionally reported a very brief smarting, which occurred in weeping areas immediately after application of the ointment. In practically all cases the itching was so relieved that the patients no longer scratched, and in many cases itching was no longer present at all.

If it was to occur, definite improvement in the eruption was noted within a week in all cases. Once improvement became evident it was progressive but usually reached a peak within four weeks. Even though no more improvement occurred in most patients after that time, they could be maintained in an improved condition and were content to continue treatment even though they made no further progress. Actual relapse during treatment was noted only rarely.

It may be seen from table 1 that 3 of the patients were treated with the ointment alone. In addition to these there were 3 patients who received phenindamine tartrate orally together with tars locally before a supply of the phenindamine phosphate ointment arrived. From these patients we could conclude with reasonable certainty that phenindamine tartrate administered orally was of little or no benefit in this disease and that the ointment was almost entirely responsible for the improvement seen.

Figures 2 and 3 illustrate the degree of histologic clearing which occurred in 1 of the patients of this group (D. S.). The first photomicrograph was made from a specimen taken for biopsy from the right antecubital space before treatment with phenindamine was begun. The second specimen, also from the right antecubital space, was taken, after two weeks of treatment, from an area which initially had shown identical involvement. The patient was an 11 year old girl who had had a constant, severe, disseminated neurodermatitis for ten years.

The control series of 7 patients were treated in various ways, as noted in table 1. Except in the case of 1 patient who had a mild eruption on the face (F. B.), treatment with the ointment base was of no benefit, while treatment with phenindamine promptly caused improvement. Figure 4 shows the result of one week of treatment in 1 of the control patients (J. R.) with the ointment base applied to the right forearm and phenindamine phosphate ointment to the left.

A patient with disseminated neurodermatitis was treated locally with the compounds Nu-1326 and Nu-1525. One of the compounds was used in the antecubital space on one side and the other in the opposite space. After one week a very slight decrease in itching was noticeable in the area treated with Nu-1326, and no change at all was attributable to Nu-1525. After this treatment the patient received phenindamine therapy, with prompt improvement.

Circumscribed Neurodermatitis.—As was stated previously, the results obtained with phenindamine in the treatment of the series of patients with circumscribed neurodermatitis were not as satisfactory as those secured in the other group. Data referable to the treatment of patients with circumscribed neurodermatitis are recorded in table 2.

Circumscribed neurodermatitis was treated as satisfactorily with phenindamine as with any other topical medication and with the added

TABLE 1.—*Data on the Treatment with Phenindamine of Patients with Disseminated Neurodermatitis*

Patients Treated with Phenindamine

Patient	Age	Degree of Eruption	Duration of Eruption	Regions Affected (Bilaterally)	Length of Treatment	Results of Treatment in Percentages of Improvement		Reaction
						Subjective	Obective	
D. S.	11 yr.	Severe	10 yr.	Eyelids, neck, wrists, popliteal and antecubital fossae	3 wk.*	More than 75%	More than 50%	None
J. S.	15 yr.	Severe	15 yr.	Eyelids, neck, wrists, popliteal and antecubital fossae	7 wk.*	More than 75%	More than 50%	None
L. C.	16 mo.	Moderate	15 mo.	Antecubital and popliteal fossae	1 wk.*	More than 50%	More than 50%	Insomnia
D. D.	2 yr.	Mild	22 mo.	Antecubital and popliteal fossae	3 wk.*	100%	100%	Insomnia, irritability
D. H.	8 yr.	Moderate	4 yr.	Antecubital fossae	7 wk.*	None	None	None
M. R.	11 yr.	Severe	2 wk.	Face, neck, antecubital and popliteal fossae	5 wk.*	100%	More than 75%	None
R. G.	8 mo.	Severe	6 mo.	Face, neck, antecubital and popliteal fossae	6 wk.*	More than 50%	More than 50%	Insomnia
D. F.	5 yr.	Moderate	7 mo.	Neck, antecubital and popliteal fossae	5 wk.*	More than 50%	More than 50%	None
K. F.	18 yr.	Mild	17 yr.	Face	3 wk.*	100%	More than 75%	None
E. P.	42 yr.	Severe	5 mo.	Face, neck, antecubital fossae	2 wk.*	More than 75%	More than 75%	None
S. F.	6 mo.	Severe	5 mo.	Face, neck, wrists, popliteal and antecubital fossae	4 wk.*	More than 75%	More than 50%	Insomnia
D. C.	22 yr.	Severe	4 yr.	Face, neck, antecubital and popliteal fossae	3 wk.*	100%	More than 75%	None
T. E.	9 mo.	Moderate	2 mo.	Face	3 wk.*	More than 25%	More than 50%	None
J. P.	3 yr.	Moderate	30 mo.	Face, neck, antecubital and popliteal fossae	3 wk.†	More than 75%	More than 75%	None
F. A.	6 mo.	Moderate	4 mo.	Face	2 wk.*	None	None	None
E. W.	52 yr.	Moderate	3 yr.	Face	3 wk.*	More than 50%	More than 50%	None
E. T.	24 yr.	Severe	20 yr.	Face, neck, antecubital and popliteal fossae	2 wk.*	None	None	None
S. G.	7 mo.	Moderate	6 mo.	Face, antecubital and popliteal fossae, legs	1 wk.†	More than 50%	More than 50%	None
A. S.	48 yr.	Severe	2 mo.	Face, neck, arms	7 wk.*	More than 75%	More than 75%	None
C. G.	3 yr.	Mild	2 yr.	Antecubital and popliteal fossae	5 wk.*	100%	100%	None
C. D.	44 yr.	Moderate	14 yr.	Face, axillas	1 wk.*	More than 50%	More than 50%	None
G. K.	22 yr.	Mild	9 yr.	Antecubital fossae	3 wk.*	More than 75%	More than 75%	None
E. A.	37 yr.	Moderate	6 yr.	Antecubital and popliteal fossae	3 wk.†	Worse	None	Itching worse after 1 week

Control Patients

Patient	Age	Degree of Eruption	Duration of Eruption	Region Affected (Bilaterally)	Length and Type of Treatment	Results of Treatment in Percentages of Improvement	
						Area Treated with Phenindamine	Control Area
W. B.	18 mo.	Moderate	1 yr.	Antecubital and popliteal fossae	3 wk.; phenindamine to left side and ointment base to right side	More than 50%	No change
D. C.	13 yr.	Moderate	3 yr.	Neck, antecubital fossae	2 wk.; phenindamine to left side and ointment base to right side	More than 75%	No change
J. R.	52 yr.	Severe	18 yr.	Neck, arms	1 wk.; phenindamine to left side and ointment base to right side	More than 50%	No change
R. H.	18 mo.	Severe	6 mo.	Face, neck, antecubital and popliteal fossae	6 wk.; phenindamine ointment followed by 1 wk. with ointment base	More than 75%	Relapse with ointment base
F. B.	6 mo.	Mild	2 mo.	Face	1 wk.; ointment base	Cleared	
S. D.	19 yr.	Severe	15 yr.	Face, neck, antecubital and popliteal fossae	2 wk.; ointment base	No change	
L. B.	4 mo.	Moderate	2 mo.	Face, antecubital and popliteal fossae	2 wk.; with ointment base followed by 2 wk. with phenindamine	No change with ointment base More than 50% improved with phenindamine	

* The asterisk indicates the use of oral and local therapy.
† The dagger indicates the use of local therapy alone.

advantage that itching became reduced to absent while treatment was continued. In this disease, improvement in the appearance of the lesion often was not seen until as long as two weeks after the beginning of treatment, although itching was promptly relieved after application of the ointment. In the group with circumscribed neurodermatitis, as opposed to the other, there was a tendency for initial subjective and

TABLE 2.—*Data on the Treatment with Phenindamine of Patients with Circumscribed Neurodermatitis*

Patients Treated with Phenindamine *

Patient	Age	Degree of Eruption	Duration of Eruption	Region Affected	Length of Treatment	Results of Treatment in Percentages of Improvement: Subjective	Objective	Reactions
S. W.	56	Severe	20 yr.	Right instep	7 wk.	50% initially, relapse under treatment	50% initially, relapse under treatment	Negative reaction to patch tests
M. K.	58	Moderate	10 yr.	Nucha	3 wk.	More than 75%	More than 75%	None
B. B.	38	Moderate	12 yr.	Insteps, elbows, palms	5 wk.	100% initially, relapse under treatment	75% initially, relapse under treatment	Negative reaction to patch tests
F. M.	51	Severe	8 yr.	Right ankle	10 wk.	25% initially, relapse under treatment	25% initially, relapse under treatment	Positive reaction to patch tests
M. H.	66	Mild	5 yr.	Nucha	10 wk.	100%	Less than 50%	None
M. P.	36	Moderate	6 yr.	Right palm	10 wk.	100%	Less than 50%	None
J. N.	62	Moderate	5 yr.	Right thigh	3 wk.	100%	More than 50%	None
B. H.	55	Moderate	8 yr.	Nucha	2 wk.	More than 75%	Less than 50%	None
L. B.	46	Moderate	2 yr.	Insteps	5 wk.	100%	More than 75%	None
M. B.	58	Moderate	8 yr.	Nucha, hands	2 wk.	More than 75%	More than 50%	None
G. T.	31	Moderate	2 yr.	Scrotum	4 wk.	100%	More than 50%	None
E. W.	38	Severe	12 yr.	Nucha	6 wk.	Less than 50%	None	None
E. G.	66	Moderate	16 yr.	Nucha	3 wk.	More than 75%	More than 75%	None
E. B.	72	Mild	3 yr.	Nucha	2 wk.	Less than 50%	None	None

Control Patients

Patient	Age	Degree of Eruption	Duration of Eruption	Region Affected	Length and Type of Treatment	Results of Treatment: Subjective	Objective
J. D.	48	Moderate	6 yr.	Nucha	2 wk. with ointment base	No change	No change
T. H.	62	Severe	15 yr.	Left ankle	2 wk. with ointment base	No change	No change
B. T.	57	Moderate	11 yr.	Nucha	2 wk. with ointment base	No change	No change

* Only local medication was given to patients with circumscribed neurodermatitis.

objective improvement to be followed by relapse while treatment was continued. These patients received ointment alone, and the relief of itching seemed as great for them as for those with disseminated neurodermatitis, most of whom received both oral and local therapy.

The 3 control patients with circumscribed neurodermatitis were treated only with the ointment base, and none showed either any improvement in the appearance of the lesions or any relief of itching.

One patient with a lesion on each instep was treated with the compounds Nu-1326 and Nu-1525, one to each lesion. Although treatment

lasted only one week there was no relief of itching and no improvement in the appearance of the lesions.

Miscellaneous Dermatoses.—During the course of this study we treated a small number of patients with diseases other than neurodermatitis. Three patients with urticaria received phenindamine tartrate orally, and all 3 experienced complete relief from itching and a reduction in the size and number of the lesions present but not complete disappearance of the lesions. Several patients with pruritus vulvae and pruritus ani have been treated also, with good symptomatic relief.

Side Reactions.—Of the group of patients with disseminated neurodermatitis there were 5 who had reactions to medication. Four were infants who received phenindamine orally and locally. All 4 became restless and irritable and slept poorly. These symptoms subsided completely within twenty-four hours after the drug was discontinued by the oral route but continued locally. The fifth patient was the only one of the series who became worse during treatment. The itching of this patient became severer one week after the beginning of treatment. Patch tests gave negative results.

Three of the 14 patients with circumscribed neurodermatitis had relapses while under treatment. Since the nature of the relapse was not clear, each patient was given patch tests. One of these patients (F. M.) showed an edematous, erythematous reaction in forty-eight hours after patch testing with the phenindamine phosphate ointment. A patch test with the ointment base had negative results.

In addition to the patients reported here we have had called to our attention 1 other patient, whose reaction we consider worthy of note. This person, a patient of Dr. John Seddon, began to have insomnia after two weeks of treatment with phenindamine, 25 mg. twice daily. Because of the sleeplessness the dosage of phenindamine was reduced to 25 mg. in the morning, and the patient was given diphenhydramine hydrochloride, 25 mg. at night. The insomnia grew still more severe and the patient began to suffer from pain in the thighs and increased sweating. She remained mentally clear, but her symptoms progressed, and muscular incoordination and numbness in legs and arms increased, so that she could hardly climb stairs and began to drop kitchen utensils. There were no accompanying neurologic signs. The symptoms completely abated within three days after treatment with phenindamine was discontinued.

COMMENTS

The literature is replete with references to the use of antihistaminic drugs in disseminated and circumscribed neurodermatitis. With regard to oral administration of the previously used antihistaminic compounds it

has been generally agreed [6] that they are of some value in relieving itching but that they have no other effect on the course of the disease.

The use of these drugs in local therapy of neurodermatitis has not been as extensive. Perry [7] concluded that diphenhydramine hydrochloride applied in ointment form was of no value in neurodermatitis and of debatable value in other diseases. Feinberg and Bernstein [8] found that tripelennamine hydrochloride ointment had a favorable effect in relieving the itching of disseminated neurodermatitis; however, their findings could not be confirmed by Sulzberger and his associates.[9] One of the few favorable reports on the local use of previous antihistaminic substances in neurodermatitis was that of Sulzberger, Baer and Levin,[9] who employed tripelennamine hydrochloride ointment and reported that half of their 16 patients with circumscribed neurodermatitis showed not only a diminution of itching but also a clinical improvement. An additional 25 per cent of their patients showed transitory improvement only —a prominent feature of our own series treated with phenindamine.

The only other report of local therapy of neurodermatitis with antihistaminic drugs which seemed to be of benefit to the patient was that of Aaron, Peck and Abramson.[10] These investigators employed tripelennamine hydrochloride in an aqueous solution and introduced the drug into the skin by iontophoresis. They reported 2 cases of circumscribed neurodermatitis and 1 of disseminated neurodermatitis which greatly improved with treatment.

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6. Friedlander and Feinberg.[2] Osborne, E. D.; Jordon, J. W., and Rausch, N. G.: Clinical Use of a New Antihistaminic Compound (Pyribenzamine) in Certain Cutaneous Disorders, Arch. Dermat. & Syph. **55**:309-321 (March) 1947. Logan, G. B.: Histamine Antagonists in the Treatment of Allergic Disease in Children, M. Clin. North America **31**:948-953 (July) 1947. Baer, R. L., and Sulzberger, M. B.: Pyribenzamine in the Treatment of Itching Skin Conditions, J. Invest. Dermat. **7**:147-150 (July) 1946. Levin, S. J.: Beta-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl): Its Use in Allergic Diseases, J. Allergy **17**:145-150 (May) 1946. Friedlander, A. S.: The Use of a Histamine Antagonist, Beta-Dimethylaminoethyl Benzhydryl Ether Hydrochloride, in Allergic Disease, Am. J. M. Sc. **212**:185-191 (Aug.) 1946. Friedlander, A. S., and Friedlander, S.: Pyribenzamine in Hay Fever and Other Allergic Disorders, J. Lab. & Clin. Med. **31**:1350-1354 (Dec.) 1946.

7. Perry, D. J.: The Local Use of Benadryl Ointment, J. Invest. Dermat. **9**:95-97 (Aug.) 1947.

8. Feinberg, S. M., and Bernstein, T. B.: Pyribenzamine Ointment for the Relief of Itching, J. A. M. A. **134**:874-875 (July 5) 1947.

9. Sulzberger, M. B.; Baer, R. L., and Levin, H. B.: Local Therapy with Pyribenzamine Hydrochloride, J. Invest. Dermat. **10**:41-42 (Feb.) 1948.

10. Aaron, T. H.; Peck, S. M., and Abramson, H. A.: Iontophoresis of Pyribenzamine Hydrochloride in Pruritic Dermatoses, J. Invest. Dermat. **10**:85-90 (Feb.) 1948.

It is well known that both diphenhydramine hydrochloride and tripelennamine hydrochloride are local anesthetics; however, their failure to diminish itching when applied locally would seem to indicate that their penetrability is low, a property which is overcome to some extent by ion transfer. Phenindamine, on the other hand, is obviously able to penetrate the skin readily; and this property is apparent from both the almost invariable relief of itching and the speed with which relief occurs. One of our patients (B. B.), who had a severe disseminated neurodermatitis, repeatedly insisted that application of phenindamine phosphate ointment to her antecubital spaces was followed by an almost complete anesthesia lasting for from fifteen to thirty minutes, after which period other sensations returned but itching remained absent for several hours. Casual testing of the reaction of this patient to pinprick, during a period of anesthesia, certainly showed that the sensation of pain was much diminished. Most patients did not experience this degree of anesthesia. Admittedly, however, it is not clear to us how much of the improvement noted in these patients was due to relief of the sensation of itching and how much was due to a genuine healing effect caused by the medication employed. It has long been a generally accepted observation that patients with either the disseminated or the localized form of neurodermatitis have had improvement of the condition when their pruritus was relieved. Whatever the mechanism which resulted in the relief of the patients in our series, we can say it yielded more satisfactory results than any topical agent heretofore employed.

The most frequent reactions to phenindamine tratrate administered orally (sleeplessness and irritability) were not seen when phenindamine phosphate was applied only locally. The sedative effects of diphenhydramine hydrochloride and tripelennamine hydrochloride, while being desirable on occasions, are also important as occupational hazards [11]; the danger accompanying the use of those drugs is obviated by the local use of phenindamine.

CONCLUSIONS

A new antihistaminic drug, phenindamine, is discussed.

This drug is chemically unrelated to and pharmacologically distinct in many of its effects from previously employed antihistaminic compounds.

The results of the use of phenindamine in the treatment of circumscribed and disseminated neurodermatitis and other itching dermatoses are presented and discussed.

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11. Slater, B. J., and Francis, N.: Benadryl: Contributing Cause of Accident, J. A. M. A. **132**:212-213 (Sept. 28) 1948. Arnold, H. L.: Benadryl in Chronic Urticarias, Arch. Dermat. & Syph. **54**:71 (July) 1946.

It is believed that the use of this drug represents a significant advance in the treatment of neurodermatitis, as improvement can be obtained with local therapy alone. This form of treatment has been entirely free from constitutional reactions, and we have encountered only 1 case of induced sensitivity. In our hands, phenindamine ointment seems to be the best drug available for the treatment of disseminated neurodermatitis. In the treatment of circumscribed neurodermatitis, though beneficial in most cases, it was not as effective as in that of the disseminated disease.

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STUDIES OF SWEATING

II. On the Mechanism of Action of Local Antiperspirants

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AND
FRANZ HERRMANN, M.D.
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ALTERATIONS of sensible perspiration are known to occur under the influence of the autonomic nervous system (e. g., stimulation after injection of pilocarpine or acetylcholine and inhibition through the use of atropine, through degeneration of peripheral nerves, and by use of local anesthetics). Moreover, the alterations occurring during the course of certain clinical diseases (e. g., miliaria rubra [prickly heat] and tropical anhidrotic asthenia) have recently received intensive study.[1] But little is known of the mechanism involved in the modifications of sweat secretion which are routinely produced through topical remedies, such as the common topically applied "antiperspirants."

In fact, there is somewhat more information concerning the process of topical stimulation of sensible perspiration. In recent clinical, experi-

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Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., Coronado, Calif., April 28, 1948.

From the Skin and Cancer Unit, Department of Dermatology and Syphilology (Dr. Marion B. Sulzberger, Director), New York Post-Graduate Medical School, New York University-Bellevue Medical Center.

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mental and histologic studies, O'Brien [1e] elucidated the increased excretion of eccrine sweat through local application of wool fat. Similar observations had been made by P. G. Unna [1f,g] and later by Wolpert [1h] and by Rothman [1i]; and we could confirm O'Brien's observations in our own investigations. The provocatory action of the hydrophilic fats on sensible perspiration is, according to O'Brien, intimately related to the degree of patency of the sweat pores, the size being increased or maintained in the presence of these fats on the surface of the skin.

The reverse of this process, namely, narrowing of the openings of the sweat ducts, is generally regarded as the cause of decreased or inhibited sweating under the influence of the widely used antiperspirant preparations. Pharmacologists and dermatologists quite uniformly ascribe this effect to the astringent properties of the active ingredients, this ascription applying equally whether the preparation contains aluminum salts, zinc salts, formaldehyde or resorcinol. Occasionally also the adsorbent action of the metal salts in use is mentioned as an effective mechanism.

It was our hope that histologic examinations might shed some light on the mechanism of action of these topical antiperspirants, especially on the more or less hypothetic and experimentally unproved conception of a merely dehydrating and astringent action. It is the object of this report to give some very preliminary information on histologic observations of the skin of grossly normal axillas of healthy persons after the application of several commonly employed antiperspirant creams.

METHOD

The exact history of each person being tested was taken with special reference to the intensity of sensible perspiration and the previous use of antiperspirants, for example. A considerable interval had to precede the test applications of the antiperspirant in those instances in which an antiperspirant preparation had been used previously. For each application an amount of the preparation of approximately the volume of a pea was used, gently rubbed in with the finger tips as is customary. On 8 men three applications to each axilla tested were made at twelve hour intervals before the biopsy specimen was taken. No washing was allowed in the interim in these cases, but taking of a specimen for biopsy was always immediately preceded by removal of the remnants of the cream with water and by careful, soapless shaving. On 3 of these men an antiperspirant cream of the following formula was applied.

Formula A

Waxy components: glycol stearates and stearic acid	12%
Emulsifying agents: solution of sodium alkyl benzene sulfonates (W-102)[2]	8%
Hydrated aluminum sulfate	20%
Inert filler	13%
Water	47%

2. W-102 is produced by Wallace Laboratories, Inc., 53 Park Place, New York.

Three other men used a cream the composition of which is as follows:

Formula B

Waxy components: glycol stearates and stearic acid	16%
Emulsifying agents: solution of sodium alkyl benzene sulfonates (W-102)[2]	4%
Light liquid petrolatum U. S. P.	2%
Hydrated aluminum sulfate	20%
Inert filler	13%
Water	44%

Two other men used both formulas, one in each axilla.

Formula A was found by clinical observations and electrohygrometric determinations (by means of a special electrohygrometer [11d]) to be much more effective in reducing sensible perspiration than was formula B.

Preparation A was used by an additional subject (female) once daily in "routine fashion" for two consecutive weeks before a biopsy specimen was taken from the axilla. Another person (male) used preparation A in a single application on the armpit one hour before a biopsy specimen was taken (after preceding electrohygrometric examinations had shown that the beginning of antiperspirant action was manifest in this case within forty minutes after the application). On 2 control persons the vehicle of preparation A was applied to the axillas in three consecutive applications prior to biopsy, just as on the 8 test persons.

All biopsy specimens were cut completely in serial sections, after fixation in Bouin's fluid and embedding in paraffin.

RESULTS

None of the subjects exhibited any gross, clinically discernible, alteration, irritation or inflammation at the sites where the antiperspirant creams were applied. In several instances, in particular after the use of formula A, antiperspirant activity was distinctly noticeable at the time of the removal of tissue for biopsy. A definite reduction of sensible perspiration had occurred in the woman who had used preparation A for two consecutive weeks.

HISTOLOGIC OBSERVATIONS

In striking contrast to the absence of any clinical irritation, a considerable inflammatory reaction in the cutis of each specimen was revealed at microscopic examination. This reaction was distinctly more pronounced after the application of formula A than after the use of formula B. It should be stressed at this point that all the other alterations, such as degenerative changes of the sweat apparatus, to be described later, were likewise definitely less after the application of preparation B than after that of the stronger antiperspirant, A.

In the axillas of 2 control subjects who had received applications of the blank vehicle of preparation A, and in the axillas of persons who had received no applications, the characteristic changes were absent.

ECCRINE GLANDS

The cellular elements of the inflammatory reaction consisted—in conformity with what might be expected, considering the short duration

of the application—primarily in polymorphonuclear leukocytes with varying admixtures of lymphocytes. These cells appeared to be attracted to the area of the uppermost portion of the eccrine sweat ducts,

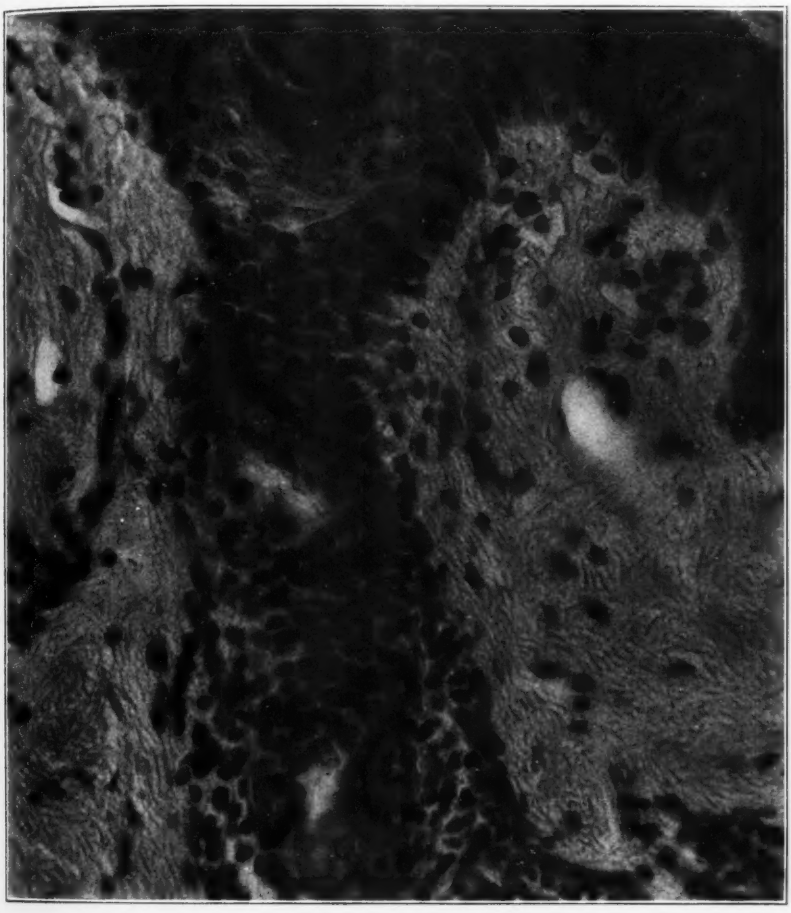

Fig. 1.—Eccrine pore after application of antiperspirant preparation A, showing acute inflammation of duct and neighboring vessels (high power dry lens).

perhaps by the positive chemotaxis of the material or its derivatives that had entered through the sweat pore. As these cells were of hematic origin, it goes without saying that the vessels of the upper corium frequently were the site of perivascular inflammation.

From the foregoing statements it is clear that at a somewhat later stage enough inflammatory cells will have worked their way through the epithelial barrier to appear in large numbers in the lumens of the

Fig. 2.—Two eccrine ducts after application of antiperspirant A (low power view). They are inflamed, and the one on the left is greatly dilated.

sweat ducts. Whether their presence in this location acts as a barrier to the outflow of sweat is a matter of conjecture.

There was no evidence of narrowing of sweat pores.

It should be emphasized at this point that in the majority of biopsies the changes just discussed were not seen in all eccrine ducts but in a sizable percentage, which varied from case to case. It is interesting to note that the changes in the eccrine glands were confined to the

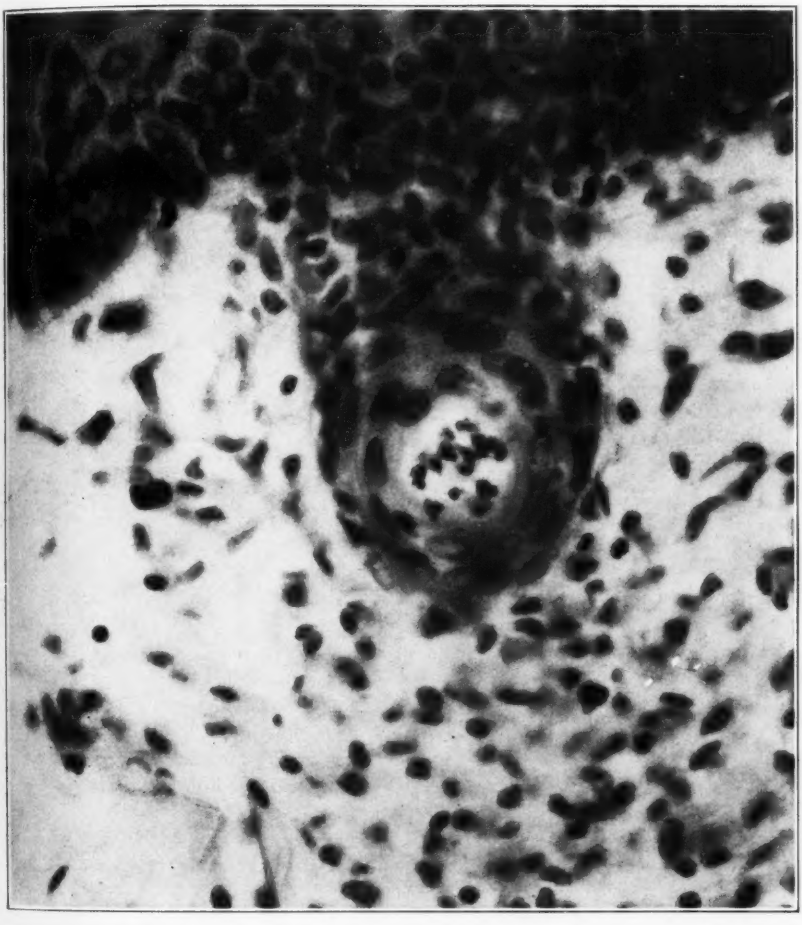

Fig. 3.—Eccrine duct after application of antiperspirant A, showing inflammatory cells which have penetrated into the lumen (high power dry lens).

straight portion of the ducts. In 5 biopsies (4 persons) an occasional eccrine gland and duct was seen to have appreciable diffuse dilatation. The significance of this observation is not clear as yet.

APOCRINE GLANDS

In the apocrine glands, as in the eccrine pores, there was nowhere any evidence of a narrowing of the ostiums of the ducts. In other respects, however, the observations for the apocrine glands, which—as

Fig. 4.—Apocrine gland after application of antiperspirant A, showing the expulsion of nucleoli from the nuclei (oil immersion lens).

is well known—open into hair follicles above the level of the sebaceous glands, were of an entirely different nature.

One of the earliest changes observed in otherwise normal-appearing apocrine glands was expulsion of the nucleolus into the cytoplasm of the cells of the acini. This was followed soon by dissolution of the nucleus (caryolysis) or by its pyknosis. If the damage to the lining

cells was severe enough, they disintegrated, leaving a denuded membrane behind.[2a]

Desquamated lining cells, apparently washed away by the secretory pressure, appeared as cellular casts in various portions of the gland.

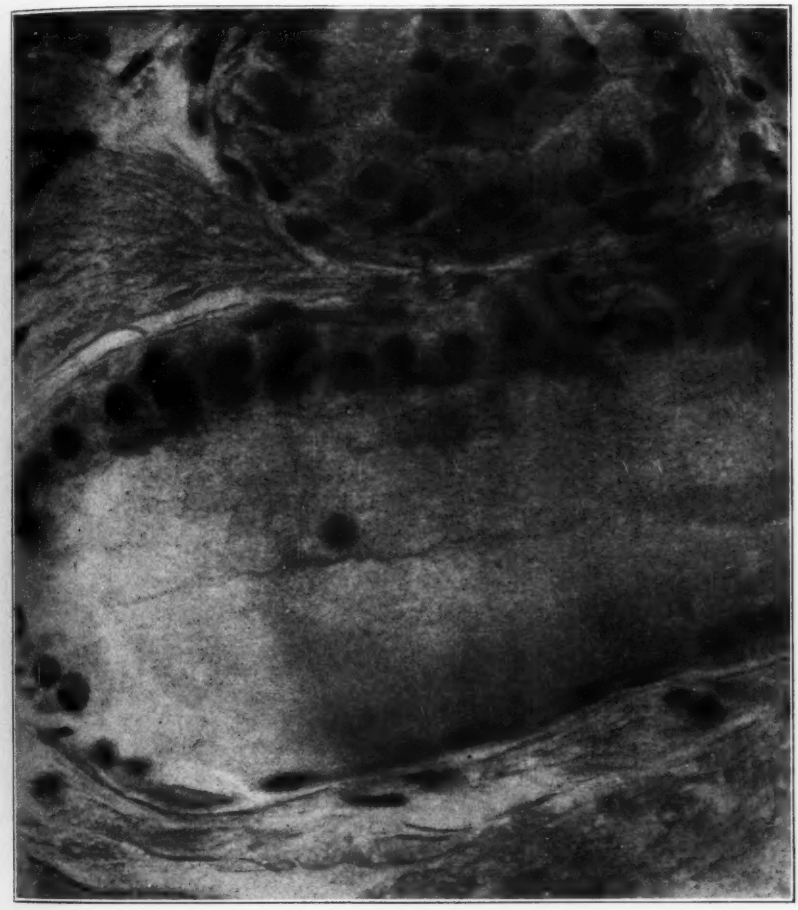

Fig. 5.—Apocrine gland, after application of antiperspirant A (high power dry lens). The section of the tubule at the bottom evidences disintegration of epithelium, while the section at the top contains cellular casts.

2a. The lining of the aprocrine gland is much more likely to show regressive changes and detachment from its basement membrane than is that of the eccrine gland, a fact which makes postmortem study of normal control material unsatisfactory.

This process frequently involved one gland and spared the one immediately adjacent.

The cast material, which might well act as a mechanical obstacle to the outpouring of sweat, not rarely appeared to have been carried with the sweat stream, so to speak, and eventually lodged in the

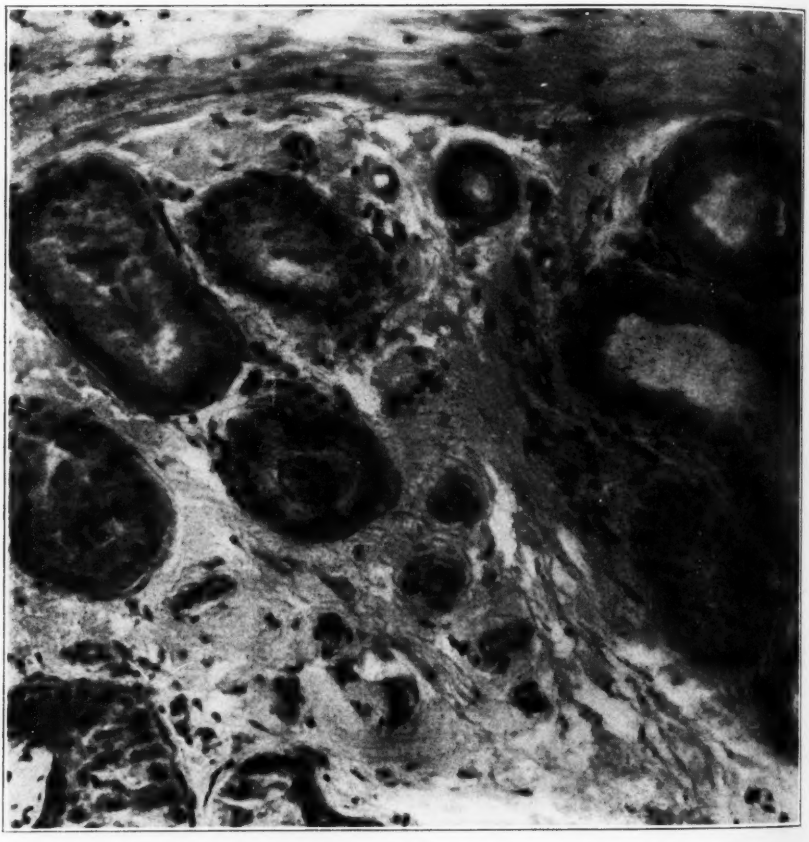

Fig. 6.—Apocrine glands after application of antiperspirant A (high power dry lens). The acini on the left show numerous cellular casts in their lumens, while the group on the right appears normal.

perpendicular portion of the apocrine duct. From the foregoing observations it is clear that, in contrast to what was observed in the eccrine glands, the main changes in the apocrine glands occurred in the secretory tubule. Changes in the duct were secondary.

An occasional mitotic figure was seen in an apocrine duct, while mitosis of apocrine gland cells was missing. This absence of regeneration is to be expected to be seen in short term experiments like ours.

All the alterations, inflammatory and degenerative, described in the foregoing paragraphs were observed very early indeed and were already present to the full degree in the biopsy specimen taken one hour after a single application of formula A.

COMMENTS

Perhaps the least expected, but at the same time the most distinct and uniform, observation in these histologic studies is the invariably present inflammatory reaction.

For practical reasons it may be pointed out that the presence of this microscopically observed inflammation does not indicate that antiperspirant preparations are more harmful than they are generally considered to be. For millions of people are using these products effectively and without suffering any harm. On the other hand, the generally known occasional appearance of clinical inflammatory reactions under the influence of antiperspirants is readily understood in the light of our observations.

The other unexpected, though clear, result of our histologic investigations is the discovery that the usual assumption of an astringent action of antiperspirants, with consequent narrowing or collapse of the openings of the sweat ducts, finds no support whatsoever in our microscopic studies. With our technic it was seen that most, if not all, of the ostiums were wide open after use of the preparations.

Although our present histologic observations give no single, simple explanation of the mode of action of the antiperspirants used in these experiments, it appears probable that the described inflammatory reaction and degenerative alteration of the sweat glands are involved in the mechanism of the decrease of sensible perspiration. This assumption is in agreement with the fact that a weaker inflammatory response was observed microscopically after application of the less effective antiperspirant preparation, B, than was seen after use of the more effective formula, A—and the absence of the characteristic changes in the control specimens.

One of the most conspicuous changes which may explain diminished sweat excretion in the axillas is the described degenerative alteration of the apocrine glands. Because of this there are certainly less cells available for sweat production. The fact that the degenerative process is manifest in the apocrine coils rather than the eccrine glands, where the inflammatory process prevails, is readily understood when one considers the much greater frailty of the apocrine glands. While the

degeneration does not become apparent in every apocrine gland, the proportion of visibly damaged glandular elements is considerable.

Not only the alteration of the epithelium but also the desquamation of these lining cells into the lumens of the ducts might have a bearing on the impaired delivery of sweat on the surface. It is conceivable that this castoff material acts as a plug in the ducts. Furthermore, the possibility cannot be denied that the concentration of inflammatory elements around an eccrine duct may produce a stenosing, flow-obstructing ring.

From these considerations it is evident that additional investigations are needed to clarify further the mechanism of antiperspirant action. At present it appears possible, or even probable, that several interdependent or independent factors contribute to the effect.

The conspicuous infiltrative inflammation around and through the epithelium of the eccrine ducts, and even into their lumens, and likewise the almost selective degeneration of elements of the apocrine glands are highly suggestive of a special chemotaxis of the active antiperspirant ingredients. It is possible that aluminum soaps are formed by interaction of the applied aluminum sulfate and some of the fatty acids along the ducts and that this process brings about the described changes. An interesting and also most unexpected clinical observation is not inconsistent with the aforementioned assumption. After the application of the antiperspirant preparation and before demonstrable decrease of sensible perspiration, one can observe an individually variable period during which there is actually a provocatory effect on the excretion of sweat. Similar to the effect obtained after application (and removal) of wool fat,[1e] increased production of sweat can be demonstrated with the starch-iodine test in this early phase following application of the antiperspirant formula.

We shall not here describe in detail the occasional clinical inflammatory reactions we have observed after the use of antiperspirants in general. However, it may be noteworthy that such reactions are observed chiefly or only in persons with strong axillary perspiration, who feel the need of using antiperspirants. We also find it noteworthy that we have repeatedly seen these relatively rare reactions occurring in several members of a family, e. g., in mother and son, and in a father and his two daughters. More observations are needed to decide whether or not this familial occurrence is only coincidental.

SUMMARY

Twelve biopsy specimens were taken from the axillary skin of healthy volunteers after application of two antiperspirant preparations containing aluminum sulfate as the active ingredient. All the specimens were cut serially. There were distinct reactive alterations in the cutis.

These changes were much more pronounced after the application of the more effective of the two preparations and were absent in the control specimens. The essential histologic observations were as follows:

In the eccrine sweat glands there was considerable cellular infiltration through the epithelium of the perpendicular portion of the ducts, together with perivascular cuffing in the upper corium (polymorphonuclear leukocytes and lymphocytes).

In many of the apocrine sweat glands there were degenerative alterations of the lining of a great part of the acini (tubules), with conspicuous desquamation of epithelial cells and formation of cellular casts.

There was no narrowing or collapse of the ostiums of the ducts of either eccrine or apocrine glands.

Possible implications of these data for an explanation of the mode of action of antiperspirants are discussed, and the need for further investigations is emphasized.

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ABSTRACT OF DISCUSSION

DR. FREDERICK G. NOVY JR., Oakland, Calif.: Dr. Sulzberger and his co-workers are to be congratulated on continuing their valuable investigations on the disturbances of sweating in various diseases.

In the past there had been no truly investigative work done on antiperspirants. It had been assumed that the action of antiperspirants is an astringent one, causing narrowing of the sweat ducts or actual temporary stenosis of the sweat ducts so that less perspiration reaches the skin and thus there is a reduction of sweating. Today, Dr. Sulzberger has clearly shown from his histologic studies that this is not the case. He has demonstrated that with the eccrine glands there is an inflammatory infiltrate about the duct. This inflammation tends to narrow the duct orifice so that less perspiration is produced. The glands themselves are not affected.

In the case of the apocrine glands there is a degeneration of the secretory cells, which in turn causes a decreased production of their fluid. This degeneration of the cells of the apocrine gland occurs rapidly after death, so that some of the changes could be explained on the basis of the death of cells. On the other hand, Dr. Sulzberger has clearly shown in his histologic observations that there are cellular casts along with the degeneration, which combination tends to produce plugging of these glands.

These findings are quite different from those of Dr. Sulzberger and his coworkers in prickly heat, thermogenic anhidrosis and the sweat retention syndrome. In these three conditions decreased production of sweat was due to actual plugging of the duct orifices by keratinized material and hyperkeratosis surrounding the duct opening. Again, in cases of postquinacrine dermatitis, Dr. Sulzberger found that a different condition prevailed to cause the decrease in sweating. In the latter condition, the failure to sweat existed because of actual atrophy and destruction of the sweat ducts due to the severe inflammation caused by the quinacrine dermatitis.

It is interesting to note that there is a decided clinical difference between the effectiveness of formula A and that of formula B. Chemically the difference between these two formulas is that formula B contains 2 per cent more light petrolatum and an increased amount of waxy substances. With this small increase in the amount of light petrolatum, the aluminum sulfate was not effective and little or no antiperspirant effect was noted.

The degeneration of the apocrine glands might well account for the fact that these antiperspirants also have a deodorant effect, because most of the odor of the axilla and the pubic area is due to these glands.

This investigation is fundamental and of extreme importance for a better understanding of disturbances in sweating.

DR. SAMUEL M. PECK, New York: Dr. Sulzberger deserves a great deal of credit for undertaking this work. Time and again, those of us who have had to discuss the action of antiperspirants before various government agencies have had to rely on theoretic explanations for the actions of these materials. This is the first time that I have had the pleasure of having presented to me factual material concerning the action of the antiperspirants on the skin and an explanation of what actually occurs when perspiration is diminished. I should like to have Dr. Sulzberger explain to me the mechanism by which abscesses are formed after the use of antiperspirants. After hearing the paper and seeing the histologic changes, I conclude that perhaps it would be better for one to use a deodorant instead of an antiperspirant to eliminate body odors.

DR. HERMAN SHARLIT, New York: Frankly, I was somewhat shocked to see these observations at the clinic. I watched these experiments, and I can assure you that every procedure was used to make this report correct. I want to present a point of view with respect to the meaning of these data which should be taken into consideration. It is properly what might be anticipated, that the application of a new, concentrated metallic salt to the skin would do a certain amount of damage in some way. This report gives the evidence of the damage. Certain physiologic factors show that there was apparently a slowing up of the rate of sweat production. That slowing up is not necessarily due to the pathologic changes evidenced here. It is known that this slowing up is maintained. Therefore, it would be necessary to demonstrate that by continual use of this material one would continue to give evidence of this type of infiltration mechanically produced. It might be that the person becomes inured to this irritant and that the reaction would not persist. Dermatitis, pustulation and papulation occur, and use of the preparations must usually be given up. Commercial manufacturers do not by any means distribute most of the antiperspirants. Women give a prescription of their own, in which aluminum chloride is used, to their druggists. As for the matter of deodorizing, I don't think that these compounds do any good. One simply masks one odor with a stronger one.

DR. JOHN BELISARIO, Sydney, Australia: I should like to start by asking Dr. Sulzberger if he would tell what the actual vehicle was that was employed. When I discussed miliaria rubra with O'Brien, who performed and wrote the first work on this subject in connection with tropical anhidrosis and hyperkeratosis of the mouths of the sweat glands, he informed me that the wool fat employed did not stimulate sweating but rather made the keratin permeable, so that the sweat dammed back could permeate to the surface. I believe this explanation to be correct.

I very much appreciated the paper; it is really a fine piece of work and should help a great deal in the elucidation of this subject. This paper is in keeping with

all of Dr. Sulzberger's work on the subject, which has been outstanding and is admired by us in Australia.

DR. MARION B. SULZBERGER, New York: I thank Dr. Novy and the rest of you for your kind and pertinent discussions.

Like Dr. Novy, we too were astonished by the radical changes in effects produced by what seems to be but a minor change—not in the "active ingredient," but only in the vehicle employed. But that result is in entire accord with what I have seen in relation to the effects of vehicles of many topical agents, including such diverse agents as various local medicaments, insect repellents, protective films and ointments against poison gases or agents used on the skin or in wounds for bactericidal or fungicidal effects: A slight alteration in the vehicle chosen can make a tremendous difference in the effects achieved.

I am particularly happy to hear Dr. Peck's remarks. If, as we suspect, the changes seen under the microscope in our studies are actually pictures of the principal mechanism through which the antiperspirant effects of these agents are brought about, then in the future the biopsy and the microscopic pictures may provide one of the objective ways of studying the effectiveness of antiperspirants of this type.

As far as Dr. Peck's question regarding the sweat gland abscesses, or rather, the apocrine gland abscesses, is concerned, no such abscesses were produced in any of our 10 test subjects. However, it is well known that, as Dr. Peck states, the clinical use of antiperspirants is sometimes (fortunately most rarely) followed by sweat gland abscesses in the users. The mechanism of the formation of such abscesses may perhaps be explained by the pictures we found. It is noteworthy that, as a result of our interest in these problems, we found in our great clinical material in which antiperspirants were used only 5 cases of sweat gland abscesses; and it is most remarkable that these 5 cases all occurred in two families, 2 in one family (mother and son) and 3 in another family (father and two daughters). Of course these figures are insufficient to permit one to draw conclusions, but it seems to me conceivable that the tendency to sweat gland abscesses may be in a measure dependent on local anatomic or functional anomalies of the sweat glands and that these anomalies can well be hereditary and thus of familial occurrence.

In reply to Dr. Sharlit's generous remarks, all we can now say is that the changes we have described are the only ones we saw which could account for the reduction of sweating after the local use of these antiperspirants. There are still great gaps in our knowledge here, and our studies are being continued. All we now know about the time intervals concerned is that the changes observed can appear as early as sixty minutes after one application of the antiperspirant and that in the few cases studied thus far the changes had disappeared on histologic examination two weeks after the last application of an antiperspirant. Moreover, it seems that the same changes can occur in persons who use antiperspirants habitually as took place in those volunteers who in the course of our present studies used them for the first time.

I thank Dr. Belisario for his kind words. With the exception of the light petrolatum added in formula B, all the ingredients in both formulas were the same —such as the same wetting agent and the same fillers—but the proportions of "fats" and wetting agent were somewhat different. I shall be glad to give Dr. Belisario further details if he wishes them and to tell him where he can obtain the exact specifications.

What Dr. Belisario said about Dr. O'Brien's fine work and the action of wool fat is absolutely correct. Wool fat does act differently from many agents

previously used to produce local outpouring of sweat; it probably acts by clearing the pore openings and by hygroscopic action on the sweat in the ducts.

It must be obvious to all physicians why we at the Skin and Cancer Unit and Department of Dermatology and Syphilology of the New York University-Bellevue Medical Center have been and continue to be so interested in the mechanisms and pathologic changes of sweating. Sweating and aberrations of sweating are of profound importance both in dermatology and in many other branches of medicine. What my co-workers and I have recently labeled "the sweat retention syndrome" can lead to pricking and itching and scratching, to vesicle formation (dyshidrosis, miliaria) and to inflammation, when the sweat which should normally be poured out on the skin's surface is blocked and remains within the tissues and either forms pools and vesicles around the sweat glands or trickles through into the surrounding tissues. When the quality of sweat being absorbed is great, there can be toxic manifestations, local lymph node enlargement and perhaps other local and general effects. Moreover, the failure of the normal mechanism of cooling by the outpouring and evaporation of sweat can lead to a variety of general medical disturbances which may have profound temporary or lasting effects on the respiratory, cardiovascular and nervous systems. All the symptoms of this syndrome are likely to be most pronounced when non-secretory evaporation of fluid is not sufficient to cool and when secretory sweating is called on continuously or repeatedly, as is the case in workers and worriers in constantly hot and humid environments. I believe that one of the main reasons why so many patients with a variety of cutaneous eruptions—for example, atopic dermatitis, various eczematous and eczematoid eruptions, dyshidrosis and certain fungous infections (not to speak of asthma, sinusitis and arthritis and other nondermatologic diseases)—so often do well in a dry, even-temperatured environment and when freed from "tensions" may well be that under these last-mentioned conditions these persons do not so often require sweat secretion in order to cool and to lose fluid and are therefore largely freed from the sweat retention syndrome.

One more suggestion in closing—many drugs, foods and other absorbed agents and metabolites normally may be wholly or partially excreted in secreted sweat. When the pore is blocked, all these are not excreted but retained in—one might even say "injected into"—the tissues. I should like you to think about the possible consequences of these literally millions of intracutaneous injections per day (adult man has an estimated 2,000,000 sweat pores) in relation to allergic sensitization and desensitization phenomena and to allergic diseases, for example, allergic eruptions due to drugs such as quinacrine or the eczematoid eruptions which sometimes exacerbate on exposure to foods or inhalants, e. g., atopic dermatitis and perhaps other eczematoid dermatoses of the hands.

I thank you all again for your attention and encouragement, and I hope that my collaborators, Dr. Franz Herrmann and Dr. Frederick Zak, and others of my department will soon have more to report on this subject of aberrations of sweating.

Clinical Notes

MALIGNANT DYSKERATOSIS, ERYTHROPLASIA OF QUEYRAT TYPE

Report of a Case

WILLIAM E. McDANIEL, M.D.
AND
LESTER M. MASON, M.D.
CINCINNATI

Erythroplasia is a malignant dyskeratosis of unknown etiology, first described in 1893 by Fournier and Darier,[1] who designated it as épithéliome papillaire. The name erythroplasia was suggested in 1911 by Queyrat,[2] who described in detail several cases of what appeared to be an identical condition. Sulzberger and Satenstein[3] reported the first case in the American literature in 1933; we have found accounts of 18 additional cases, for the most part in society transactions (table).[4] This report adds 1 more case to the slowly growing number.

From the Department of Dermatology and Syphilology, the University of Cincinnati College of Medicine, and the Cincinnati General Hospital.

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4. (*a*) Smith, L. M., and Hughes, R. D.: Erythroplasia of Queyrat, South. M. J. **32**:731 (July) 1939. (*b*) Irgang, S., and Alexander, E. R.: Erythroplasia of Queyrat in a Negro, Arch. Dermat. & Syph. **34**:247 (Aug.) 1936. (*c*) Hall, T. B.; Hoffman, R. L., and Newman, R.: Erythroplasia of Queyrat and Carcinoma of Glans Penis: Report of Case, Urol. & Cutan. Rev. **39**:21 (Jan.) 1935. (*d*) Stiles, F.: Erythroplasia of the Glans Penis, Arch. Dermat. & Syph. **30**:647 (Nov.) 1934. (*e*) Schwartz, H. J.: A Case for Diagnosis (Erythroplasia of Queyrat?), ibid. **30**:594 (Oct.) 1934. (*f*) Erythroplasia of Queyrat? case presented by Dr. E. B. Tauber and other members of the Department of Dermatology of the University of Cincinnati College of Medicine and the Cincinnati General Hospital, ibid. **34**:160 (July) 1936. (*g*) Throne, B.: A Case for Diagnosis (Erythroplasia of Queyrat?) ibid. **29**:633 (April) 1934. (*h*) Fox, H.: Erythroplasia, ibid. **32**:357 (Aug.) 1935. (*i*) Schiller, A. E.: A Case for Diagnosis, ibid. **36**:929 (Oct.) 1937. (*j*) Rosenthal, T.: Erythroplasia of Queyrat, ibid. **35**:1176 (June) 1937. (*k*) MacKee, G. M.: A Case for Diagnosis (Erythroplasia?) ibid. **46**:592 (Oct.) 1942. (*l*) Friedman, R.: A Case for Diagnosis (Erythroplasia of Queyrat?), ibid. **41**:1192 (June) 1940. (*m*) Callaway, J.: Erythroplasia of Queyrat, ibid. **42**:350 (Aug.) 1940. (*n*) Schmidt, O. E.: Erythroplasia of the Penis, ibid. **42**:673 (Oct.) 1940. (*o*) Rosen, I: Erythroplasia of Queyrat, ibid. **42**:981 (Nov.) 1940. (*p*) Combes, F. C.: A Case for Diagnosis (Erythroplasia of Queyrat?), ibid. **38**:802 (Nov.) 1938. (*q*) Freeman, H. E., and Engler, J. E.: A Case for Diagnosis: (Kraurosis Penis? Erythroplasia of Queyrat?) ibid. **43**:206 (Jan.) 1941. (*r*) La Rocco: Erythroplasia of Queyrat, ibid. **40**:456 (Sept.) 1939.

Cases of Erythroplasia of Queyrat as Reported in the American Literature

Authors	Race, Sex and Age	Total Duration of Lesions	Evidence of Malignant Degeneration	Evidence of Circumcision	Evidence of Syphilis	Treatment and Results
Sulzberger and Satenstein [3] (Presented by Lapowski * 2 yr. later and by Lapowski and Walzer [5] 6 yr. later)	W M 39	9¾ yr.	None	No mention	None	Filtered and unfiltered roentgen rays; no improvement; electrocoagulation; recurrence in 3 to 4 mo.
Smith and Hughes [4a]	Mexican M 24	1½ yr.	None	Yes	None	Electrocoagulation and solid carbon dioxide; small area of recurrence after 9 mo.
Irgang and Alexander [4b]	Negro M 77	5½ yr.	None	?	None	Electrocoagulation; no recurrence after 14 mo.
Hall, Hoffman and Newman [4c]	W M 61	2 yr.	Squamous cell	No	Yes	Amputation of penis and removal of inguinal lymph nodes
Stiles [4d]	W M 42	Unknown	None	No	Yes	Electrocoagulation; no follow-up
Schwartz [4e]	W M 31	4 mo.	None	?	None	?
Tauber [4f]	Negro M 38	6 yr.	None	No	None	?
Throne [4g] (Presented by Lapowski * 5 mo. later and by Lapowski and Walzer [5] 5 yr. later)	Jew M 29	6¼ yr.	None	?	None	Electrocoagulation on two occasions; recurrence
Fox [4h]	W M 25	10 mo.	None	?	?	?
Schiller [4i]	W M 36	3 wk.	No biopsy	No	Yes	?
Rosenthal [4j]	W M 62	6 to 7 yr.	Basal cell carcinoma	No	None	?
MacKee [4k]	W M 70	10 to 15 yr.	Yes	?	None	Bland local therapy; progressive roentgen irradiation; amount unknown; no benefit
Friedman [4l]	W M 38	1½ yr.	No biopsy	?	None	?
Callaway [4m]	W M 24	1 yr.	None	?	?	Bismuth intramuscularly and filtered roentgen rays; no benefit
Schmidt [4n]	W M 69	2½ yr.	Yes	No	None	Filtered roentgen rays; no benefit
Rosen [4o]	W M 24	3 yr.	None	?	None	?
Combes [4p]	W M 39	2 yr.	Yes	No	None	Bismuth intramuscularly and bland local therapy; no benefit
Freeman and Engler [4q]	W M 62	7 yr.	None	No	None	Filtered roentgen rays; no benefit
LaRocco [4r]	W M 53	2½ yr.	None	?	None	Antisyphilitic therapy; no benefit

* Lapowski, B.: Erythroplasia of Queyrat, Arch. Dermat. & Syph. **33**: 160 (Jan.) 1936.

of cells of the epidermis. Some portions showed spotty hyperkeratosis and parakeratosis. In some regions there were definite wildness and disturbances of cells, with intraepidermal squamous cell malignant change. Other rete plugs showed portions of irregular mitosis with numerous dyskeratotic cells. In the dermis there was an extensive lymphocytic and plasma cell infiltrate; in many portions the infiltrate extended into the rete plug and produced miliary abscesses. There was pronounced edema, with separation of the collagen fibers. No tumor masses were seen in the dermis.

The cause of this entity is unknown. Certain predisposing conditions are recognized; chief among these is an inherited predisposition to develop cutaneous malignant changes, e. g., a rough, dry skin. Chronic irritation is undoubtedly a factor; Lapowski and Walzer[5] were cognizant of this fact and employed protection from irritation by a metal tubular shield in treating 2 cases. In the

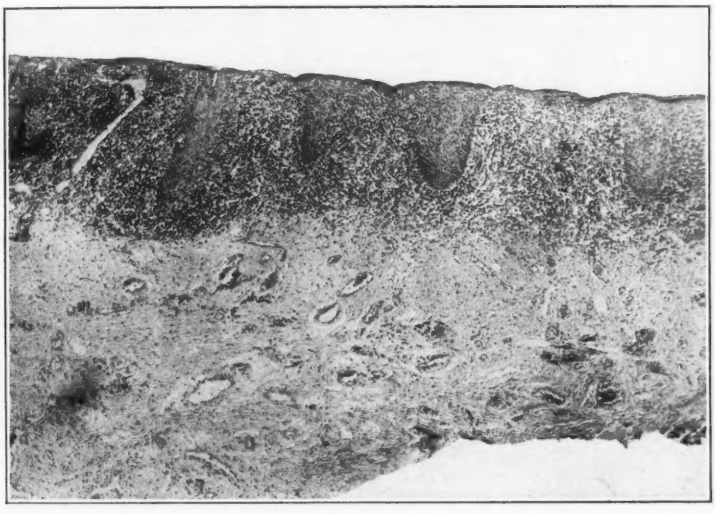

Fig. 2.—The irregular acanthosis, elongated and broadened papillae and the pronounced edema and vascular dilatation in the corium should be noted. The intense cellular infiltrate is sharply demarcated below. (Hematoxylin and eosin stain; × 40.)

European literature syphilis has often been mentioned as an etiologic factor. Cases reported in the American literature have not borne this out, however; in only 3 of the cases was there evidence of syphilis; in our case there were no indications of the disease. The question of uncircumcision in etiology seems to have been largely neglected by previous authors, reports of 9 of the 19 cases containing no information on this point. There was 1 case in which circumcision had been performed, and another in which it seemed likely that it had, the patient being a Jew. In 8 of the cases the patient was uncircumcised.

5. Lapowski, B., and Walzer, A.: Erythroplasia of Queyrat, Arch. Dermat. & Syph. **39**:184 (Jan.) 1939.

REPORT OF CASE

History.—T. R., an unmarried white man aged 71, was first seen in the dermatologic clinic of the Cincinnati General Hospital on Jan. 10, 1947; he was referred from the genitourinary clinic (where he was being treated for multiple urethral strictures) because of a persistent erythematous patch on the dorsum of the glans penis. The lesion was of three months' duration and asymptomatic; it had been first noticed as an erythematous spot, centrally located on the dorsum of the glans penis, in October 1946. At that time the lesion had been the size of a small pea and nonelevated; it gradually enlarged peripherally, but the patient was little concerned because of a lack of symptoms.

Nothing pertinent was elicited from the family or personal past history. The patient has been retired on a pension for fifteen years. Prior to his retirement he had worked for thirty years as a street cleaner and street repairer, and for eighteen years as a carriage driver. There was no history of syphilis, diabetes or ingestion of drugs.

Fig. 1.—The sharp margination of the lesion and the dry, erythematous surface may be seen. The scar near the corona is at the site of removal of tissue for biopsy.

Examination.—A sharply demarcated, irregularly rectangular, erythematous patch measuring 25 mm. by 19 mm. involved the dorsum of the glans penis and the corona; the lesion was a plaque, elevated about 1 mm. The involved area was of slightly greater firmness than the surrounding tissue and had a velvety appearance; the surface was completely dry, and the epithelium was intact. No enlarged lymph nodes were found in the inguinal regions. The lesion was nontender. The skin in general was dry and showed poor turgor; no lesions of the mucous membranes of the mouth were found.

A specimen for biopsy was taken by electrosurgery from the proximal margin of the lesion, and the bleeding base was electrocoagulated; the lesion has recurred in the scar made in the taking of tissue. No biopsy was made of the lymph glands.

The histopathologic report by Dr. Leon Goldman was as follows: The section showed irregular acanthosis with appreciable differences in the staining quality

Schreck and Lenowitz [6] studied a clinical group of 139 men with carcinoma of the penis and compared them with a control group of patients with carcinoma elsewhere. They attributed the differences in incidence to variations in sex hygiene.

The differential diagnosis of erythroplasia of Queyrat may at times be difficult. The lesions are well defined, infiltrated areas with shiny, red, velvety surfaces which may be moist or dry, slightly elevated or flat. The commonest site is the

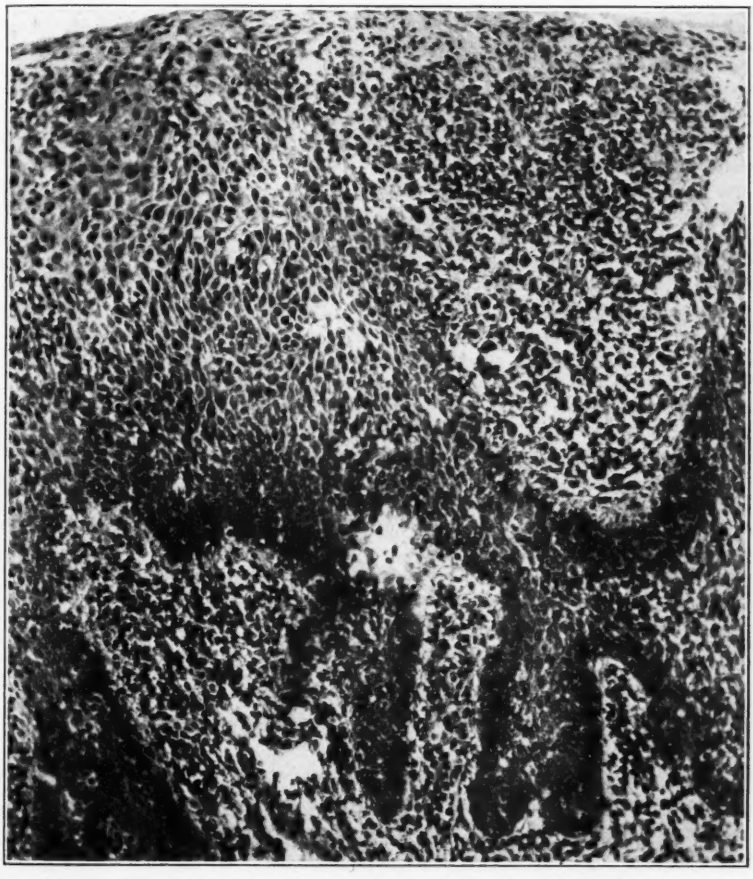

Fig. 3.—There is appreciable irregular downgrowth of the rete pegs and differences in the staining quality of cells of the epidermis. (Hematoxylin and eosin stain; × 160.)

6. Schreck, R., and Lenowitz, H.: Etiological Factors in Patients with Carcinoma of the Penis and in Control Groups, Am. J. Path. **22**:637 (May) 1946.

glans penis and foreskin. All cases reported in the American literature have been in men. Other reported sites of involvement are the scrotum; the vulva, the buccal mucosa, including the tongue and the lips; the cheek, and the back.

The differential diagnoses include Bowen's disease, Paget's disease (carcinoma simplex of nipple), leukoplakia, kraurosis, lupus vulgaris (tuberculosis luposa), eruption due to drugs, psoriasis, eczema, syphilid and lichen planus. Darier pointed out that in cases clinically identical, dyskeratotic changes which are definitely of the type of Bowen's disease have been found. If the conception of Civatte is accepted, erythroplasia is nothing more than Bowen's disease of the mucous membranes. Clinically, crusting is regularly present in Bowen's disease but not necessarily in erythroplasia; histologically, Ash [7] stated the belief that there is more fibrosis present in erythroplasia than is seen in either leukoplakia or Bowen's disease.

Extramammary cases of Paget's disease occur (this observation has been disputed by some persons); Busman and Woodburne [8] reported a case involving the glans penis. The histologic picture of Paget's disease is typical, however. The absence of apple jelly nodules should serve to exclude tuberculosis luposa. An eruption due to drugs, a patch of psoriasis of eczema or of lichen planus or a syphilid can usually be ruled in or out by appropriate procedures. Distinctive exudative discoid and lichenoid dermatosis of Sulzberger and Garbe caused confusion in 1 instance. Early there is localization of this condition to the penis and the tip of the nose; later, generalized lesions appear.

The treatment of erythroplasia has been a subject for much discussion among previous authors. No form of treatment seems to be universally successful; radiation therapy has proved unsatisfactory; cryotherapy has been followed by recurrences. Endocrine therapy has not been reported. The best treatment short of radical operation appears to be complete removal, with a safe margin, by electrocoagulation.

In 5 of the 19 cases there was histologic evidence of malignant degeneration, of basal cell carcinoma in 1 instance and of the squamous cell variety in the other 4. In 1 of these cases there was regional glandular enlargement. In 12 of the cases there was no histologic evidence of malignant changes; however, usually only one biopsy specimen was taken. In 2 cases there were no biopsies. The duration of the disease in the first-mentioned group ranged from two years to twelve and one-half years, or an average of five and one-tenth years; in the group showing no evidence of malignant degeneration the range was from four months to nine and three-fourths years, or an average of approximately three and nine-tenths years. In this regard, in our case there was histologic evidence of early squamous cell degeneration with the lesion having been present but three months. There was no regional adenopathy, however.

SUMMARY

A case of erythroplasia of Queyrat with carcinoma in situ is presented and previously reported cases reviewed. The recommendation by Ash that "malignant dyskeratosis" replace "precancerosis" in terminology is advocated.

3241 Burnet Avenue.

7. Ash, J. E.: Personal communication to the authors.

8. Busman, G. J., and Woodburne, A. R.: Paget's Disease of the Glans Penis, with Central Carcinomatous Degeneration, Arch. Dermat. & Syph. **24**:396 (Sept.) 1931.

USE OF POLARIZED LIGHT IN COLOR PHOTOGRAPHY OF MUCOUS MEMBRANES

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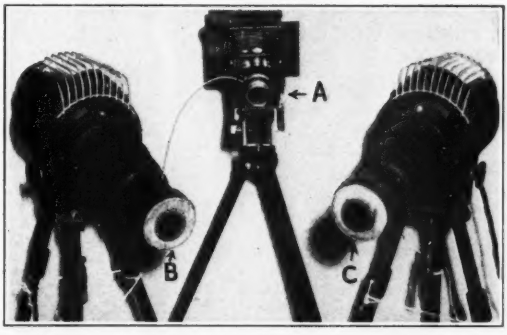
MIAMI BEACH, FLA.

Polarized light has been used for a number of years in commercial photography to eliminate glare, but, to my knowledge, after a careful search through the available literature, it has not been used for photography of lesions of the mouth. Since distracting high lights are often observed in photographs of lesions of the mouth, it was thought that a method to use polarized light would be useful.

A method was employed in which polaroid® filters were placed in the light source and over the camera lens. The filters were rotated until all glare had



Apparatus for the use of polarized light in color photography of mucous membranes. Polaroid® filters are indicated by *A*, *B* and *C*.

been eliminated from the image on the ground glass screen. This procedure, however, greatly reduced the total amount of light that reached the film. Since color film has a slow emulsion speed, it was found that a brilliant source of light was needed in order for the necessity for prolonged exposure to be overcome. This problem was met by the use of two 1,000 watt photoflood bulbs in spotlights of condensing type, as illustrated in the accompanying figure. The lights are placed 6 inches (15 cm.) from the mouth. With the setup described, the exposure is 1/25 second at *f* 8, type A kodachrome® film being used, for an image of half the object size. If a smaller image with greater depth of field is desired, either a shorter exposure or a smaller diaphragm opening can be used.

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SYPHILITIC JUXTA-ARTICULAR NODES

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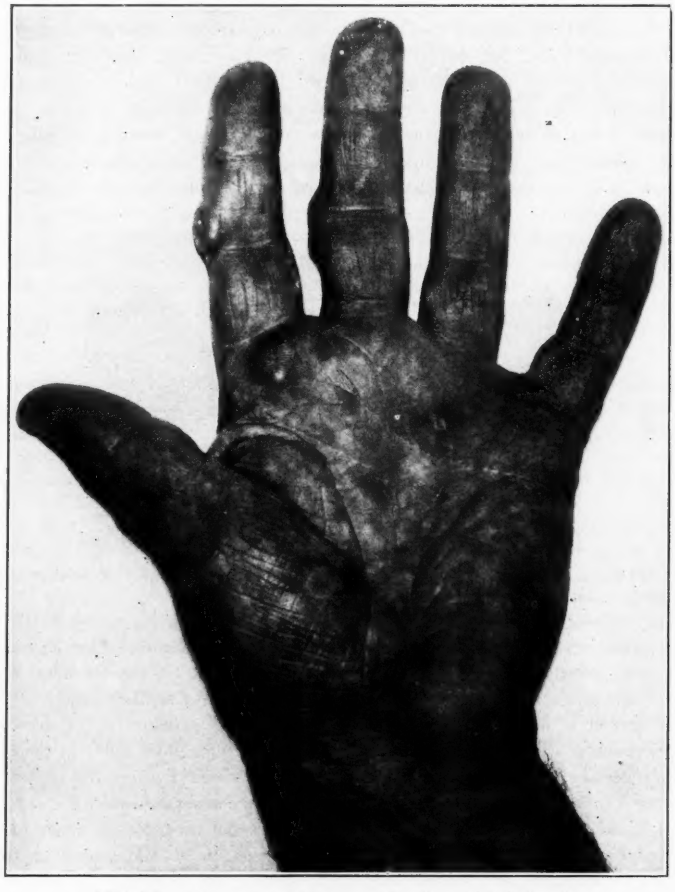
MONTREAL, CANADA

Recently, I had the opportunity of observing a patient with juxta-articular nodes. The unusual localization of these nodules warrants a short report.



Multiple nodes on the fingers and palms of left hand.

REPORT OF A CASE

A 54 year old white Canadian, unaware of his syphilitic infection, had observed during the previous four years slowly growing painless nodes on the fingers and palms of both hands. One node was removed surgically, and the diagnosis

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From the Section of Dermatology, Sub-Department of Medicine, Dr. J. C. Meakins, Physician in Chief, Royal Victoria Hospital.

of a simple fibroma was made. The patient was then referred to me, and examination revealed the following conditions.

There were numerous hard, indolent nodes on the palms of both hands and on the palmar and lateral surfaces of the fingers, about the joints. They varied in size from that of a split pea to button-like infiltrations about 1 cm. in diameter (figure). The overlying skin was normal in color and texture and was easily movable, while the nodules were fixed to the underlying structures. There were altogether seven major nodes, five of which were on the left hand. In addition, there were a number of smaller nodules, more palpable than visible, and all in the vicinity of articulations. Another node was found near the left elbow. There were no signs or symptoms of activity of the syphilitic infection. The cardiovascular system was normal on both clinical and roentgenologic study, and the neurologic examination revealed no abnormalities. The reaction to the Wassermann test of the blood was positive in a dilution of 1:196, and the reaction to the Kahn test was positive. The patient had to leave town and was referred to his physician with the diagnosis of late syphilis.

We obtained permission to reexamine the previous biopsy specimens and submitted the slides to Dr. P. H. Hartz, pathologist in chief of the Netherlands Public Health Services in Curaçao, who has had the opportunity of seeing and examining many such cases, who happened to be in Montreal at the time. He reported observations as follows:

"The main feature is the presence of thick bundles of collagen, with occasional lymphocytes, and of areas of cellular infiltration containing large fibrocytes, histiocytes and lymphocytes, forming occasional loose mantles of perivascular infiltration. However, there were dense perivascular infiltrations in the border region between the nodules and the surrounding loose connective tissue, consisting of lymphocytes and plasma cells.

"In a fibroma with collagenous bundles of comparable thickness, one would expect a more uniform appearance and absence of inflammatory changes. The presence of areas of such thick bundles of collagen together with zones of cellular infiltration is characteristic of many of these juxta-articular nodes. The absence of intimal thickening makes it difficult to establish histologically the diagnosis of syphilis, but it is known that intimal thickening is by no means a regular finding in these nodes."

SUMMARY

Multiple juxta-articular nodes on the fingers and palms of a white Canadian are described. The histologic changes in this case are characteristic of the condition, showing thick collagenous bundles with alternating zones of cellular infiltration.

1414 Drummond Street.

EFFECT OF DIPHENHYDRAMINE HYDROCHLORIDE (BENADRYL®) ON HERXHEIMER REACTION AFTER USE OF PENICILLIN

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DETROIT

It is an established fact that, in the treatment of syphilis, penicillin causes Jarisch-Herxheimer reactions. Moore[1] stated that, perhaps to an even greater

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This investigation was carried out at the Detroit Intensive Treatment Center, Herman Kiefer Hospital; Loren W. Shaffer, M.D., Director.

1. Moore, J. E.: Penicillin in Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1946, p. 55.

extent than with arsenic, penicillin produces a true Herxheimer reaction and suggested that it occurs in 60 per cent of the patients treated. This reaction tends to manifest itself as a febrile one rather than as a mucocutaneous flare-up.

In early syphilis the Herxheimer reaction is of little consequence, but in patients with late syphilis, in which the syphilitic activity may be located in vital structures, the Herxheimer reaction is potentially dangerous.[2] Likewise, this potential danger may exist for the debilitated syphilitic infant.

Olansky [3] reported 6 cases in which Herxheimer reactions followed the first injection of as little as 1,000 units of sodium penicillin. I have seen rapid deterioration in 2 cases of dementia paralytica, and Callaway and associates [4] reported exacerbation of psychoses within the first few days of treatment with penicillin. There are reported cases of disastrous outcome in the treatment of cardiovascular syphilis with penicillin by Moore,[1] Dolkart and Schwemlein [5] and Callaway.[4] However, that the Herxheimer reaction was the cause of fatal outcome was not definitely established in these cases.

Notwithstanding the suggestion by some authors that the Herxheimer reaction may be beneficial in that it simulates therapeutic inflammation, we at this center feel that prevention of this reaction in some cases of infantile congenital syphilis and late syphilis would be advantageous.

Consequently, a study was undertaken in which the use of a strong antihistaminic substance was employed in an effort to abort the Herxheimer reaction. Diphenhydramine hydrochloride (beta-dimethylaminoethylbenzohydryl ether hydrochloride [benadryl hydrochloride®]) was used. Curtis and Owens,[6] Shaffer and associates,[7] Friedlaender [8] and others have demonstrated its influence in urticaria, which may be due to liberation of histamine into the tissues. More recently, Friedlaender suggested that the action of diphenhydramine hydrochloride is one of competing with histamine at the receptor organ rather than one of chemical neutralization of histamine.

A series of 247 consecutive patients with previously untreated primary and secondary syphilis were placed on an antisyphilitic program of 3,000,000 units of penicillin injection in oil and wax U. S. P., five arsenical treatments and three bismuth treatments in a period of ten days, penicillin alone being given on the first day of treatment. In this group we observed an incidence of the Herx-

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2. Stokes, J. H., and others: Penicillin in Late Syphilis: Interim Report, Am. J. Syph., Gonor. & Ven. Dis. **29**:313, 1945.

3. Olansky, S.: The Herxheimer Reactions of Relatively Small Doses of Penicillin, J. Ven. Dis. Inform. **28**:26, 1947.

4. Callaway, J. L.; Noojin, R. O.; Kuhn, B. H.; Riley K. A., and Segerson, J. A.: The Use of Penicillin in Treatment of Syphilis of Central Nervous System, Am. J. Syph., Gonor. & Ven. Dis. **30**:110, 1946.

5. Dolkart, R. E., and Schwemlein, G. X.: The Treatment of Cardiovascular Syphilis with Penicillin, J. A. M. A. **129**:515 (Oct. 13) 1945.

6. Curtis, A. C., and Owens, B. B.: Beta-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) in Treatment of Urticaria, Arch. Dermat. & Syph. **52**:239 (Oct.) 1945.

7. Shaffer, L. W.; Carrick, L., and Zackheim, H. S.: Use of Benadryl for Urticaria and Related Dermatoses: A Preliminary Report, Arch. Dermat. & Syph. **52**:243 (Oct.) 1945.

8. Friedlaender, A. S.: Use of Histamine Antagonist, Beta-Dimethylaminethyl Benzhydryl Ether Hydrochloride in Allergic Disease, Am. J. M. Sc. **212**:185, 1946.

heimer reaction, as evidenced by a febrile reaction, within the first twelve hours after the initial injection of 300,000 units of penicillin in oil and wax (oxophenarsine hydrochloride U. S. P. [mapharsen®] having been instituted on the second day), of 31.1 per cent (77 patients).

After treatment of the aforementioned group, we placed the next 40 consecutive patients with previously untreated primary and secondary syphilis under the same regimen but gave 100 mg. of diphenhydramine hydrochloride orally with the initial injection of 300,000 units of penicillin in oil and wax and 50 mg.

TABLE 1.—*Frequency of Herxheimer Reactions*

	Number of Patients					Number of Herxheimer Reactions				
	Total Number of Patients	Primary Syphilis		Secondary Syphilis		Total Number	Primary Syphilis		Secondary Syphilis	
		Male	Female	Male	Female		Male	Female	Male	Female
Without Diphenhydramine Hydrochloride	247	93		154		77	34		43	
	...	74	19	73	81	..	29	5	19	24
With Diphenhydramine Hydrochloride	40	14		26		19	5		14	
	...	12	2	10	16	..	5	0	3	11

TABLE 2.—*Percentage Incidence of Herxheimer Reactions*

	Without Diphenhydramine Hydrochloride	With Diphenhydramine Hydrochloride
Incidence of Herxheimer reaction.....	31.1	47.5
Male patients.....	32.6	36.3
Female patients.....	29.0	61.1
Patients with primary syphilis.....	36.5	35.7
Patients with secondary syphilis.....	27.9	53.8

of diphenhydramine hydrochloride every four hours thereafter for a total of four doses. The incidence of the Herxheimer reaction, as evidenced by a febrile reaction, was found to be 47.5 per cent (19 patients, or nearly half). The detailed analysis of these cases may be seen in tables 1 and 2.

Conclusion.—As a result of this experience, we feel that diphenhydramine hydrochloride (benadryl hydrochloride®) has no effect in preventing or alleviating the Herxheimer reaction in early syphilis when pencillin injection in oil and wax is used.

SQUAMOUS CELL EPITHELIOMA AND PSORIASIS

P. W. HANNAY, M.B., Ch.B.
EDINBURGH, SCOTLAND

Instances of epithelioma arising on areas of skin affected by psoriasis are unusual, and for this reason the following case is reported.

REPORT OF A CASE

History.—A man aged 45, an engineer, acquired psoriasis in 1922. The disease has been active ever since except for three months' remission in 1930 during a trip to Canada. In 1938 the patient discovered that arsenic medication controlled the eruption, and he had been taking solution of potassium arsenite U.S.P. (liquor arsenicalis B.P.), 3 to 10 minims (0.19 to 0.62 cc.) three times daily, with only an occasional discontinuance of the drug for a month at a time. The patient's daughter also suffers from psoriasis.

In 1942 the patient noted that his palms and soles were becoming "crusted and thickened," that his skin was becoming darker and that an ulcer was developing on a large patch of psoriasis situated on the lower left quadrant of the abdomen. The ulcer slowly enlarged and was diagnosed as a squamous cell epithelioma in 1943. The tumor was removed by surgical excision on May 25, and, as there was an enlarged inguinal node on the left side, high voltage roentgen therapy was given. Biopsy of the tumor confirmed the clinical diagnosis of squamous cell epithelioma.

The patient was first seen at the skin department of the Royal Infirmary, Edinburgh, on June 7, 1946, because of an ulcer which had been present for ten months on the left sacral region.

Examination.—General physical examination revealed nothing abnormal apart from the following dermatologic condition: There were large, scaly, leathery patches of psoriasis over the patient's trunk and limbs; there was profuse scaling of the scalp, and the finger nails showed typical psoriatic pitting. The palms and soles showed a pronounced diffuse hyperkeratosis. The whole of the trunk, the limbs, the neck and the face were deeply pigmented in a "raindrop" pattern. Pigmentation, atrophy and telangiectases were present over both inguinal regions as a result of the previous roentgen treatment given to that area.

Situated over the sacral region was a large isolated patch of psoriasis of leathery texture. To the left of the midline in the upper gluteal region, and well within the borders of the psoriatic patch, was an ulcerated fungating tumor measuring 4 cm. in diameter; it was freely movable over the deeper tissues. There was no enlargement of the inguinal nodes (fig. 1). Reactions to the Wassermann and the Kahn tests were negative.

Report of Biopsy.—The section showed two types of lesions (fig. 2). To the right of the section there was a squamous cell epithelioma with an ulcerated surface; the tumor, which was in genetic relationship with the epidermis, invaded deeply and penetrated beyond the limits of the biopsy specimen. In some areas there was well marked cell nest formation, while in others the cells were less well differentiated. Mitoses were moderately numerous. There was

From the Department of Dermatology, the University of Edinburgh Faculty of Medicine.

Fig. 1.—Fungating tumor in the center of a psoriatic patch. The "raindrop" pigmentation of the surrounding skin is faintly visible.

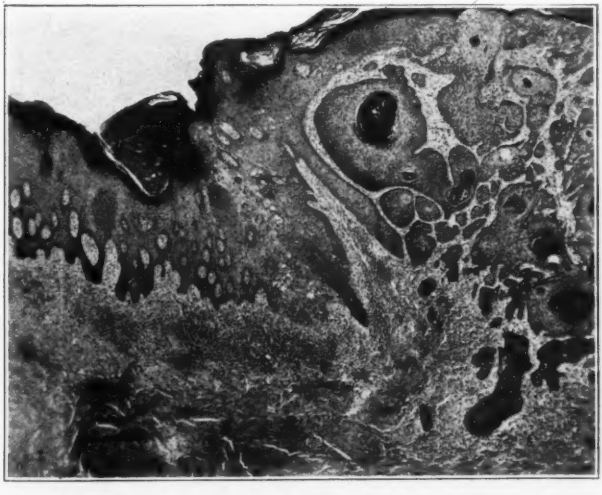

Fig. 2.—Junction area between the tumors, on the right, and the psoriatic patch on the left (× 25).

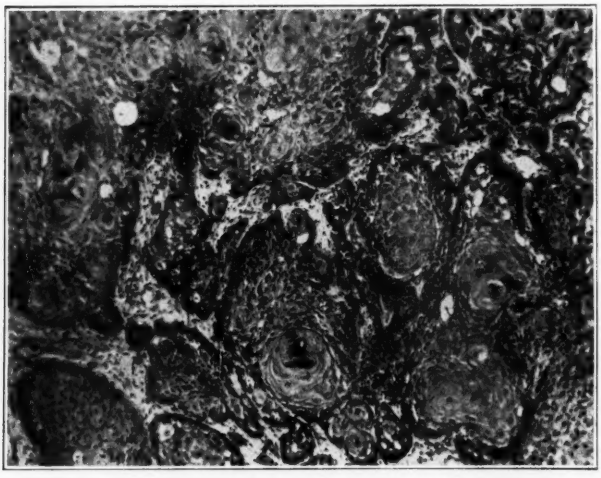

Fig. 3.—Higher power view of the epitheliomatous area, showing cell nest formation (× 70).

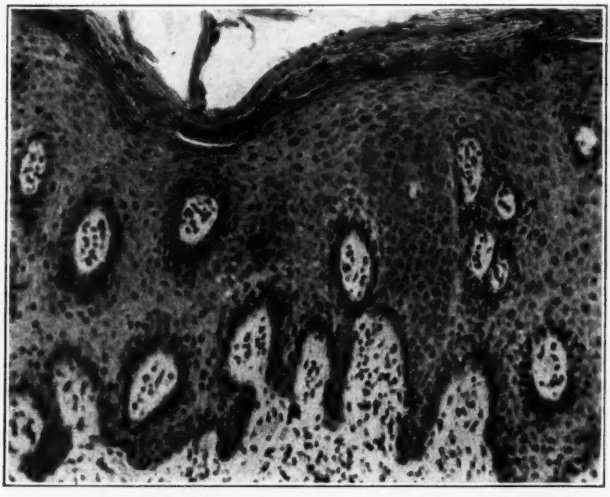

Fig. 4.—Higher power view of the psoriatic portion (× 100).

surprisingly little secondary inflammatory reaction in the surrounding tissue in view of the clinical features of the lesion (fig. 3).

To the left of the section the adjoining non-neoplastic skin showed the features of psoriasis (fig. 4). Unfortunately, the sections were cut on the slant and so did not accentuate the elongation and ballooning of the papillae, the tips of which approached the surface closely. The papillary vessels were dilated, as were those of the subpapillary region; there was a diffuse cellular infiltration, consisting mainly of lymphocytes in the subpapillary layer, and a few cells penetrated the epidermis. The epidermis was acanthotic; the stratum granulosum was thinned or absent throughout, and there was decided parakeratosis.

Treatment.—The tumor was removed by surgical excision on July 17. The psoriasis responded to treatment with salicylic acid (3 per cent) and ammoniated mercury (3 per cent) in petrolatum, followed by application of paste of crude coal tar and, finally, crude coal tar. The hyperkeratoses responded satisfactorily to dressings of equal parts plaster of lead oleate N. F. and petrolatum. The patient was discharged as well on September 10, with strict instructions never again to use arsenic. He was later seen on Jan. 22 and on March 20, 1947; the psoriasis had returned but was controlled with a tar paste (1 per cent); the area of excision showed no neoplastic recurrence, and there was no enlargement of the regional lymph nodes. On the second visit it was noted that the palmar hyperkeratoses were becoming troublesome, and treatment with lead compounds and petrolatum was again prescribed.

SUMMARY OF THE LITERATURE

A large proportion of the cases of epithelioma which have been reported as arising on psoriatic patches have been of the basal cell variety, and many of the patients had been using arsenic compounds over long periods. Gray's case [1] was an example in point: A basal cell epithelioma arose on a chronic patch of psoriasis situated in the gluteal cleft of a patient who had been using arsenic preparations for years and yet showed no other signs of reaction to the drug.

The case reported by Fordyce [2] was stated to be of a rodent ulcer, but no histologic report was given. As the patient subsequently died of metastases in the mediastinal nodes and internal organs, it is probable that the tumor was either squamous or basisquamous in type. White's report [3] is interesting mainly for the excellent summary of the views held at that time (1885) concerning the development and histologic structure of psoriatic lesions; the tumor in question was a squamous cell epithelioma. Charache [4] reported a case of squamous cell epithelioma with no known history of the administration of arsenic, while Hövelborn [5] reported a similar type of lesion in a patient who gave a history of the ingestion of arsenic.

1. Gray, A. M. H.: Brit. J. Dermat. **23**:325, 1912.

2. Fordyce, J. A.: The Pathology of Malignant Epithelial Growths of the Skin, J. A. M. A. **55**:1624 (Nov. 5) 1910. This report did not state definitely whether or not the epithelioma arose on a psoriatic patch.

3. White, J. C.: Am. J. M. Sc. **89**:163, 1885.

4. Charache, H.: Squamous Cell Epithelioma in Psoriatic Patches, Arch. Dermat. & Syph. **38**:241 (Aug.) 1938.

5. Hövelborn, K.: Dermat. Wchnschr. **101**:858, 1935.

The remaining cases reported [6] were all of basal cell epithelioma arising on psoriatic patches, and in every case the psoriasis had been present for years. Some of the patients gave a history of having taken arsenic preparations and some did not.

Wright and Friedman's paper [7] on psoriasis and its relation to multiple superficial epithelioma covered the subject fully, despite the fact that in none of the cases presented in it were the two types of lesion superimposed. These authors also stated that arsenical epithelioma which develops in persons with psoriasis almost invariably arises independently of any patch of that disease, a view which was also expressed by Ormsby and Montgomery.[8]

Details concerning the histochemical technic for determining arsenic in normal and in tumor tissue may be found in the papers published by Osborne [9] and Osterberg,[10] while the histopathologic aspect of arsenical epithelioma was fully discussed by Montgomery in two papers [11]; the discussion following one of them [11a] also contained useful comments and inferences concerning Osborne's method for determining arsenic *in situ*.

T. C. Dodds prepared the illustrations.

22 Nile Grove (10).

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6. Hutchinson, J.: Arch. Surg., London **9**:223, 1898. Hartzell, M. B.: Am. J. M. Sc. **118**:265, 1899. Whitfield, A.: Brit. J. Dermat. **18**:40, 1906. Sequeira, J. H.: Diseases of the Skin, ed. 4, New York, The Macmillan Company, 1927, p. 558; ibid., ed. 5, 1947, p. 680 (reference to Gray's case [1]). Flint, E. R., and Gordon, J.: Brit. J. Surg. **16**:321, 1928.

7. Wright, C. S., and Friedman, R. J.: Psoriasis and Multiple Superficial Epithelioma, Arch Dermat. & Syph. **27**:70 (Jan.) 1933. Franks, A. C., and Barner, J. S.: Basal Cell Epithelioma in a Psoriatic Patch, ibid. **55**:375 (March) 1947.

8. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, pp. 284 and 746.

9. Osborne, E. D.: Microchemical Studies of Arsenic in Arsenical Pigmentation and Keratoses, Arch. Dermat. & Syph. **12**:773 (Dec.) 1925; in discussion on Montgomery.[11b]

10. Osterberg, A. E.: J. Biol. Chem. **76**:19, 1928. Flint, E. R., and Gordon, J.: Brit. J. Surg **16**:321, 1928

11. (a) Montgomery, H., and Waisman, M.: J. Invest. Dermat. **4**:365, 1941: (*b*) Montgomery, H.: Arsenic as an Etiologic Agent in Certain Types of Epithelioma, Arch. Dermat. & Syph. **32**:218 (Aug.) 1935.

PARAFAVUS RESTRICTED TO THE SCROTUM

Report of a Case

EDWARD P. CAWLEY, M.D.
AND
ROBERT H. GREKIN, M.D.
ANN ARBOR, MICH.

Although most dermatologists in this country know of favus and are familiar with its manifestations, relatively few of them have been afforded an opportunity to see or study a case of parafavus or pseudofavus.

Two views of the scrotum, showing numerous scutula. These were composed exclusively of filaments and spores.

Favus, a recalcitrant, inflammatory fungus-instigated cutaneous eruption which may involve the scalp, glabrous skin and nails, is endemic in Eastern Europe. Yellow, cup-shaped crusts, or scutula, are a spectacular, though not invariable, feature of the disease. Achorion schoenleini is the classic etiologic agent, the

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name Achorion having originally been assigned to a limited number of species of fungi which produced cups.[1]

Weidman has pointed out that parafavus, as contrasted with true favus, is accompanied with scutula in small numbers, these usually being confined to one region of the body, such as the lid, scrotum, ear or back, and that residual scarring and alopecia do not always occur. Practically all species of Achorion have been incriminated as causative agents of parafavus at various times. It is most unusual, however, for other species of fungi, such as the microspora and trichophyta, to incite such an eruption. With pseudofavus, cups do not occur, although the instigating fungus is an achorion and potentially capable of inducing the formation of scutula.[1]

REPORT OF A CASE

E. K., a 24 year old white man, was first seen by us on Oct. 14, 1947, complaining of a moderately pruritic scrotal eruption of two weeks' duration. The patient's work was such that he came in close contact with milk cattle throughout each day.

Physical examination showed normal conditions except for the cutaneous eruption. On both the anterior and the posterior aspect of the scrotum were numerous cream-colored scutula of rather uniform size, most being approximately 0.5 cm. in diameter (figure). There was an associated pungent, favus-like odor.

Microscopic examination of several of the scutula demonstrated them to be composed exclusively of filaments and spores. Several culture tubes were inoculated, with a pure growth of Microsporum gypseum (M. fulvum) resulting on each within a few days. Two weeks of topical therapy with an undecylenic acid compound resulted in complete disappearance of the eruption.

SUMMARY

A case of parafavus caused by Microsporum gypseum and restricted to the scrotum is described.

1. Weidman, F. D., in Blumer, G.: The Practitioners Library of Medicine and Surgery, New York, Appleton-Century Company, Inc., 1936, vol. 10, p. 140.

News and Comment

GENERAL NEWS

Pacific Dermatological Association Organized.—As early as May 10, 1938, the Los Angeles and San Francisco Dermatological Societies began holding combined annual meetings. These meetings were not held regularly during the war but were resumed directly after the war ended. To meet the need for a more formal organization the Pacific Dermatological Association has been organized. It is open to the members of the Los Angeles, San Francisco, San Diego, Pacific Northwest and Rocky Mountain dermatological societies and to all other properly qualified dermatologists in the western portion of the United States, including California, Oregon, Washington, Nevada, Idaho, Utah, Arizona, Montana, Wyoming, Colorado and New Mexico; in British Columbia and Alberta, Canada, and in Alaska, Hawaii and Mexico.

The present officers are as follows: president, Samuel Ayres Jr., Los Angeles; vice president, Leon Frank Ray, Portland, Ore.; secretary-treasurer, H. V. Allington, Oakland, Calif., and assistant secretary, Walter R. Nickel, San Diego, Calif.

The next meeting will be held at the Hotel del Coronado, Coronado (San Diego), Calif., on Aug. 5 and 6, 1949. It will consist of a clinical session, symposiums and presentation of scientific papers.

Revised Edition of Motion Picture Reviews Now Available.—The Committee on Medical Motion Pictures has completed the first revised edition of the booklet entitled "Reviews of Medical Motion Pictures." This publication now contains all the film reviews published in *The Journal of the American Medical Association* up to Jan. 1, 1949. It also includes a classified table of contents as well as a list of motion pictures available through the Motion Picture Library of the American Medical Association.

The purpose of the reviews is to provide a brief description and evaluation of motion pictures which are available to the medical profession. Each film is reviewed and commented on by competent authorities.

Copies are available on request from the Committee on Medical Motion Pictures, American Medical Association, 535 North Dearborn Street, Chicago 10.

Bronx Dermatological Society.—On May 19, 1949, the Bronx Dermatological Society celebrated its twenty-fifth anniversary at a dinner held at the Hotel Barbizon Plaza, New York.

Obituaries

PHYLLIS SCHUYLER KERR, M.D.

1895–1949

Our friend and colleague, Dr. Phyllis Schuyler Kerr of White Plains, N. Y., died on April 12, 1949, after a long illness. Dr. Kerr was born in New Brighton, Staten Island, N. Y. Her father was Walter Craig Kerr, president at the time of his death of Westinghouse, Church, Kerr and Company.

Before Dr. Kerr entered Rush Medical College of Chicago in 1924 she had been associated with Miss Caroline Pratt as a teacher at the City and Country School of New York city, enjoying the richness of experience with the early workers in progressive education of children. Dr. Kerr graduated from Rush Medical College in 1928 and served her internship at the State of Wisconsin General Hospital in Madison.

From 1929 to 1940 Dr. Kerr was associated with the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hosptial. From 1930 to 1935 she was office assistant to Dr. Fred Wise and Dr. Marion B. Sulzberger. She had been a practicing dermatologist in White Plains since 1936. At the time of her death Dr. Kerr was Attending Dermatologist at the White Plains Hospital; Lawrence Hospital of Bronxville, N. Y.; Tarrytown Hospital, Tarrytown, N. Y., and the Westchester Division of the New York Hospital, White Plains. She was the chief of the Women's Syphilis Clinic of the Westchester County Department of Health and a member of the White Plains City Planning Board.

Dr. Kerr was certified by the American Board of Dermatology and Syphilology in 1939 and was a member of the Society of Investigative Dermatology and the Society of Medicine of Westchester County.

She is survived by her husband, Max K. Sellers, fiction writer; her mother, Mrs. Lucy L. Kerr, and her sister, Miss Eleanor Kerr, both of New Brighton; another sister, Mrs. Vaughan Baker, of Woodbine, N. J., and a brother, Donald C. Kerr, of Cornell University, Ithaca, N. Y.

The enthusiasm and kindness which Dr. Kerr brought to her work made her a true physician, bringing courage and hope to the suffering and giving inspiration to all those associated with her. Her personality was sparkling and warm. Always modest and gentle, she carried herself with a quiet and unassuming dignity. One of her most endearing qualities was her love for people, and she gave generously of her time and effort to help those with personal, as well as medical, problems. Her courage and love of life were contagious and communicated themselves to those associated with her to such an extent that their lives, too, were enriched. Her death is a great loss, not only to the medical profession but also to humanity.

SAMUEL B. FRANK, M. D.
MARION B. SULZBERGER, M.D.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Lewis B. Robinson, M.D., *Chairman*

Samuel M. Peck, M.D., *Secretary*

April 2, 1946

Juvenile Xanthoma in an Infant Girl Aged 4 Months. Presented by Dr. Charles S. Miller.

DISCUSSION

In discussing juvenile xanthoma the question comes up as to whether the condition is juvenile xanthoma or nevoxanthoendothelioma. There was no evidence in the slides of involvement of the blood vessels or of endothelial proliferation. McDonagh in 1912 described 5 cases and used the term nevoxanthoendothelioma because he held the belief that some of the cells of the cellular mass were derived from the endothelial cells of the blood vessels. Senear and Caro reviewed the literature in 1936 and reviewed the cases of McDonagh. The histologic pictures in their cases fitted in with those described by McDonagh. They did not believe that any of the cells of the cellular mass were derived from the blood vessels, but from the reticuloendothelial system. I think that there is no question from the histologic examination in this case as to the diagnosis of juvenile xanthoma.

Progeria (?) with Erythema of Hands and Feet, Partial Alopecia, Congenital Coloboma and Osteoporosis. Presented by Dr. Helen O. Curth.

E. H., a white girl aged 6, is the second child of five. All other children and the parents are healthy, and there is no consanguinity of the parents. The child was delivered normally. At birth she showed a coloboma of the iris and choroid of the left eye and esotropia. She walked at the normal time, and dentition began at 8 months. Speech was delayed until she was 2½ to 3½ years old. Her hands and feet were red at birth. Intensification of the redness, desquamation and extreme perspiration of the palms have been observed for the past year. The child complains of pain in the hands in cold weather. Diffuse alopecia has existed since birth.

In 1945 resection of the external rectus and recession of the left internal rectus was performed in the Institute of Ophthalmology, and at Babies Hospital a biopsy of the skin of the left thigh was performed for changes showing reddish-purplish discoloration. No diagnosis had been made before this, and the biopsy was inconclusive. The sweat glands and dermal appendages were found to be normal. There is enuresis nocturna, and polyuria is rather pronounced during day, but there is no excessive drinking. The child has a craving for salt.

Examination shows a small child with pale facial skin, giving her the expression of an old woman. The hair of the scalp is sparse and fine, and there is diffuse partial alopecia. A coloboma of the left eye is present. The liver and spleen are palpable. The skin of the palms and soles is at times moist, dripping

with perspiration, and shows pronounced, more or less sharply defined erythema and mild hyperkeratosis. The erythema also involves the dorsal aspect of the terminal phalanges of the hands and tips of the toes. At times the volar surface of the fingers shows some maceration. Occasionally the hands are dry. They are always warm at room temperature. The skin of the body is normal. The anterior aspects of the legs are shiny and dry. On the buttocks are remnants of a diaper rash. The nails of the feet and hands are normal. There is complete development of the deciduous teeth, which are, however, small. The blood pressure could not be felt. The radial pulse returned at 90. Her intelligence is that of a high grade or borderline defective.

Roentgenograms taken at Babies Hospital showed the cranial cavity to be small and, in relation to the face, suggestive of cerebral hypoplasia. The bone maturation is normal; however, there is osteoporosis of all bones, and severe coxa valga is present.

Results of laboratory examinations were as follows: Arsenic was 0.12 mg. per hundred cubic centimeter; dry blood serum albumin 5.61; serum globulin 2.47; nonprotein nitrogen 32; plasma chlorides 107, and fasting blood sugar 80.

A complete blood cell count showed a hemoglobin of 84 per cent, red blood cells 4,420,000 and white blood cells 9,000, with polymorphonuclear leukocytes 69, monocytes 5, lymphocytes 22 and eosinophils 4. In later counts the monocytes and eosinophils amounted to 1 per cent only.

Results of tuberculin tests with dilutions of 0.01 and 0.1 intradermally were negative. The Kline reaction was negative. Urinalysis revealed no sugar; there was a faint trace or no albumin.

DISCUSSION

DR. DAVID BLOOM: In my opinion this is a case of minor ectodermal dysplasia. The child has keratosis palmaris et plantaris, hypotrichosis and small teeth. Involvement of the sweat glands would make it a major ectodermal dysplasia, which differs from the minor one in this and also in regard to the mode of inheritance.

DR. E. W. ABRAMOWITZ: I also think that this belongs in the group of ectodermal defects, but that it is different from the anhydrotic type.

DR. A. BENSON CANNON: We all thought it more likely an ectodermal defect, for the reasons enumerated by Dr. Bloom and Dr. Abramowitz. I believe that the patient has been studied in the Babies Hospital and that the opinion of the pediatricians was that she had an ectodermal defect.

DR. PAUL GROSS: To rule out the possibility of acrodynia I referred the patient to Babies Hospital. This diagnosis was considered because of the intense redness of the palms associated with excessive sweating. The keratosis of the plams and especially the absence of neurologic symptoms were against the diagnosis of acrodynia.

DR. HELEN O. CURTH: The child has no pains in the arms and hands, and this would also speak against acrodynia. She has no ectodermal defect. She perspires normally and suffers from increased perspiration of the palms and soles. The teeth are small but complete. Ectodermal dysplasia would affect only male subjects. She does not suffer from the type described by McKay and Davidson, which shows disturbance of the nails and hair and which occurs in men and women. In this case there is no heredofamilial involvement. The child has a few signs which are seen in Werner's and Rothmund's syndromes (Thannhauser, S. J.: *Ann. Int. Med.* **23**:559 [Oct.] 1945), especially some defects of the germ plasm. She has, however, no cutaneous changes, such as

scleroderma or atrophic dermatosis, and no diabetes, and there is no family history of the disease. The syndrome she exhibits fits into that of progeria of children, with the facial expression of an old woman, shortness of stature, osteoporosis and joint deformity. I would also like to point out that the child has a craving for salt and has low blood chlorides. These two features would point, perhaps, to some insufficiency of the adrenal cortex. Studies to determine whether there are any changes in the heart or vascular system will also have to be undertaken.

Purpura Annularis Telangiectodes. Presented by DR. EUGENE F. KELLEY.

A. L., a white widow aged 41, is presented from the Vanderbilt Clinic with an eruption on the hips and legs, of about two months' duration. The lesions began as small red spots that increased in size. They were distributed symmetrically and did not itch. The individual lesions were oval, from dime-sized to dollar-sized macules, bluish red, nonpigmented and telangiectatic and did not disappear on pressure. New lesions have appeared since that time on all the extremities and on the trunk. The older lesions have assumed annular form, clearing in the center with red spots on the borders. There is considerable hyperpigmentation in the older lesions. In 1933-1934 the patient was treated for pulmonary tuberculosis which was said to be arrested.

The Wassermann reaction of the blood was negative, and the blood cell count and urine were normal. The coagulation time was 4 minutes, 10 seconds and the bleeding time 2 minutes, 3 seconds. The result of the tourniquet test was negative. The blood pressure was 162 systolic and 70 diastolic.

Biopsy showed a diapedesis of red blood cells with inflammatory reaction, and slight thickening of capillaries. The sections showed purpura, and the changes were consistent with a diagnosis of purpura annularis telangiectodes (Majocchi).

DISCUSSION

DR. MAURICE J. COSTELLO: I think that most of the clinical features are lacking in the eruption which this patient presents, such as punctuate purpura, hyperpigmentation, a tendency to annular formation and scarring.

Acanthosis Nigricans (?); Follicular Dermatitis of the Back; Latent Syphilis; Adenoma of the Thyroid Gland. Presented by DR. HELEN O. CURTH.

Keratosis Follicularis. Presented by DR. PAUL GROSS.

A. R., a Cuban woman aged 33, has had a generalized cutaneous eruption since childhood. When first seen at the Vanderbilt Clinic, on Jan. 28, 1946, the eruption was present on the face, neck, abdomen, back and upper extremities. The lesions were discrete and acuminate red hyperkeratotic papules. There was some scaling on the neck, and many of the lesions were excoriated. On the dorsum of the hands and feet and on the wrists were many flat papules resembling juvenile warts. There was a diffuse yellowish keratosis of the palms. Close inspection revealed the presence of minute pores producing a resemblance to the hyperkeratotic lesions on the palms and soles seen in parakeratosis. There was circumscribed keratosis on the soles.

Biopsy of a section from the chest disclosed several isolated lesions. These were characterized by the formation of a plug of epithelial cells keratinized with retained nuclei. At least one of these proved to be at the orifice of a coil

gland duct. A few cells had the appearance of grains in corps ronds. Multilocular lacunas had formed beneath these dyskeratotic masses. The corium was edematous and infiltrated by numerous lymphocytes. The condition was diagnosed as Darier's disease.

The serum cholesterol was 229 mg. per hundred cubic centimeters. The result of the cephalin flocculation test was negative.

The patient has been taking 100,000 units of vitamin A per day, combined with 15 Gm. of soybean lecithin, and there has been considerable improvement. The eruption on the neck and shoulders, arms and chest has almost completely disappeared, and the itching has entirely subsided, as manifested by the absence of excoriations. The hyperkeratosis of the palms has diminished, but the flat warts are still present. The remaining lesions on the abdomen appear less inflammatory, but show the clinical characteristics of keratosis follicularis.

DISCUSSION

DR. FRED WISE: I accept the diagnosis on histologic grounds if they are characteristic, but I must admit that clinically I would be inclined to hesitate about the diagnosis with a short observation period. The lesions on the hands more closely simulate epidermodysplasia verruciformis. In order to obtain a histologic picture of Darier's disease in this patient it would be desirable to remove a lesion from the trunk, rather than from any other part of the body. I would say that clinically it was atypical Darier's disease.

DR. SAMUEL M. PECK: If a case of Darier's disease is followed over a period of many years one begins to understand, perhaps, dermatoses to which we give a name, but about which we know little. I could show true cases of Darier's disease in which individual lesions around the mouth and eyelids look like seborrheic dermatitis, for instance. I have seen patients with Darier's disease which is apparently under control and quiescent suddenly show an eruption which looks like benign familial pemphigus after exposure to ultraviolet rays. It seems to me that corps ronds are not the most important characteristic histologic feature. The characteristic feature of Darier's disease is its wetness or subepidermic vesicle formation. If one begins to give large doses of vitamin A, the first thing that disappears in active disease is the wetness, and then the corps ronds and grains disappear. Dyskeratosis in itself is not characteristic of Darier's disease because it occurs in other types of pathologic processes, but I do not know of this tendency to wetness, i. e., edema plus corps ronds, in any other disease. There is much that we do not know about Darier's disease; that there is a low blood level of vitamin A and that it takes an unusually large amount in some cases to bring this up to normal, that in these cases it seems that provitamin A is not metabolized and that there may be night blindness, do not explain all of the cases. The patients are sensitive to light at some time. I would like to point out that in a number of cases in which the administration of vitamin A was rushed, improvement occurred only when therapy was discontinued for a while. There can be too much of a good thing in treatment.

DR. PAUL GROSS: Dr. Wise's skepticism as to the diagnosis can be explained by the success of treatment. Before treatment was begun, the eruption was more widespread and, especially around the hair line and on the neck, it resembled seborrheic dermatitis. The eczematous appearance was further enhanced by the presence of many excoriations. The disappearance of the eruption, except for the discrete papules on the chest and abdomen, and the decrease in the thickness of the palmar keratosis signified the improvement following treatment.

Because of the effect of excessive doses of vitamin A mentioned by Dr. Peck, I decided to use smaller doses of the vitamin and tried to enhance its absorption and utilization by the addition of soybean phosphatides. A decided effect of lecithin on vitamin A absorption in human beings has been demonstrated by Adlersberg and Sobotka *(J. Nutrition* **25**:255 [March] 1943). The clinical result in this case of Darier's disease indicates that the simultaneous administration of soybean lecithin and vitamin B complex with moderately high doses of vitamin is of definite value.

Psoriasis, Xanthelasma, Xanthoma of Tendon Sheaths. Presented by DR. BEATRICE M. KESTEN and DR. PAUL GROSS.

Lichen Planus of Mouth (?); Xanthoma of Eyelids and Tendon Sheaths (Associated with Hypertensive Cardiovascular Disease), Familial Type. Presented by DR. PAUL GROSS and DR. BEATRICE M. KESTEN.

Kaposi's Sarcoma Coincidental with Pigmented Nevus. Presented by DR. EUGENE T. BERNSTEIN.

R. M., a man aged 51, was admitted to Beth David Hospital in February 1946, acutely ill, with a temperature of 105 F. A diagnosis of lobar pneumonia of the right lung was made. The white blood cells numbered 21,000 on admission, with subsquent cell counts of 17,000, 10,000 and 7,500. Sulfadiazine was administered for seven days, but, as the temperature did not fall below 104 F., penicillin was then employed. A roentgenogram showed pneumonic consolidation.

There is boardlike, blackish brown infiltration of the right leg with ulcerations, pigmented nodules in the vicinity and many infiltrated pigmented spots on the entire trunk, with some infiltrations on other parts of the body. A pigmented nevus is present on the right arm. The eruption has existed for five or six years but has caused no discomfort, pain or itching. The cutaneous changes were regarded before admission as varicose veins stasis dermatitis, and the ulcerations were ascribed to an injury.

A biopsy specimen from the leg showed numerous dilated blood vessels throughout the cutis and particularly the upper part of the cutis. Many of them were filled with blood elements. There was a diffuse cellular infiltration. The overlying epidermis was thin and flattened. The rete pegs were missing. The palisade layer was intact and contained considerable pigment. There were no other important changes in the epidermis. The cellular infiltration was composed of small round cells, wandering connective tissue cells, few angioblasts and spindle cells. There was some hemorrhage and pronounced pigmentation. The result of Perles' test was positive. The diagnosis was Kaposi's sarcoma.

A dime-sized elevated pigmented spot was excised from the right arm for biopsy. In the middle part of the cutis there was a small mass consisting of cellular elements and some pigment. There were no important changes in the surrounding cutis. The cells composing this mass were largely spindle shaped, with oval vesicular nuclei, and contained pigment. These were connective tissue nevus cells. Perles' reaction was negative. The diagnosis was blue nevus.

DISCUSSION

DR. FRED WISE: I was under the impression that several lesions on the shin were elements of pigmented, annular and atrophic lichen planus. I suggest that a biopsy specimen be taken from a lesion on the skin about 4 inches (10 cm.) below the patella.

DR. DAVID BLOOM: I agree with what Dr. Wise has said. The blackish plaque on one leg is undoubtedly the result of an old dermatitis hemostatica and varicose ulcer. The general eruption, which is of recent origin and followed pneumonia, is unquestionably lichen planus.

DR. CHARLES S. MILLER: From the photomicrographs I think that lichen planus can be definitely ruled out. I cannot rule out the possibility of dermatitis hemostatica. Dr. Bernstein tells me he did the Perles' stain and got a positive reaction. To me, that plus the fibroblastic reaction and angioblastic proliferation would indicate the inflammatory stage of Kaposi's sarcoma. I had 1 case in which there were lesions of twenty years' duration which still showed the early signs of the inflammatory stage.

For purposes of description, the histologic changes of Kaposi's sarcoma can be divided into the following stages: (1) inflammatory stage, (2) angiomatous stage, (3) angiosarcomatous stage and (4) sarcomatous stage. The photomicrographs in this case are consistent with the clinical diagnosis of Kaposi's sarcoma in the inflammatory stage. Blue nevus is a lesion in which one sees connective tissue cells producing pigment. Apparently this patient has lesions of Kaposi's sarcoma in the inflammatory stage and a blue nevus.

DR. DAVID BLOOM: I was told that the biopsy specimen was taken from the old hemostatic scar on the leg. This would explain the diagnosis of Kaposi's sarcoma as made by the pathologist. A biopsy specimen from one of the lesions on the body would surely reveal the structure of lichen planus.

DR. EUGENE T. BERNSTEIN: The interesting feature is the coincidence of Kaposi's sarcoma with a pigmented nevus which proved to be a typical blue nevus which has nothing to do with the Kaposi's sarcoma. We know today that hemorrhagic tumors may exist in the viscera without having been suspected. In this case a pulmonary infection existed but was proved to be not a Kaposi's sarcoma involvement. To me the diagnosis is unequivocally conclusive, verified by Dr. Sachs's histologic examination. The histologic features are so typical for Kaposi's sarcoma that they cannot be mistaken for any other disease.

Steatocystoma Multiplex in a Negro Woman Aged 23. Presented by DR. FRANK VERO.

Herman Sharlit, M.D., *Chairman*

Maurice J. Costello, M.D., *Secretary*

May 7, 1946

Verruca Acuminata of the Penis Simulating Carcinoma. Presented by DR. S. IRGANG.

Erythema Annulare Centrifugum. Presented by DR. ANDREW H. MONTGOMERY.

L. G., a man aged 42, registered at the department of dermatology and syphilology, New York Polyclinic Medical School and Hospital on July 2, 1945, with a recurring and ever changing eruption of eight years' duration. The appearance then was similar to that at present, but the eruption was more extensive in distribution and more bizarre in character. The patient had been attending another clinic for a few months previously, where he had received autohemotherapy and injections of bismuth compound. Results of mycologic examinations then, as now, were negative. The blood and urine showed no abnormality. Except for an occasional cold he had enjoyed good health.

The eruption began on his arms and spread to the legs. The face and trunk have been comparatively free. At present it is mainly confined to the legs and consists of rather firm nodules which spread peripherally to form rings, one border of which becomes incomplete, forming festoon-shaped patches. Resorption of part of the ring and coalescence of patches give geographic forms. At present there is one complete ring and several partial rings with spreading elevated borders and nearly normal centers. There are no vesicles, only slight scaling, and no subjective symptoms. The eruption is not seasonal.

The patient returned to the clinic on March 22, 1946, with the present outbreak. He stated that after his first visit he was well for four months. At that time he was given a mixture containing powdered rhubarb, sodium bicarbonate and cascara in peppermint water. He reported that in times past he had clear periods of a month or so. A recent attack of influenza with fever caused no change in the eruption.

DISCUSSION

DR. CHARLES WOLF: A definite diagnosis in these cases is difficult in the early stages. The lesions simulate other diseases. Over a period of years these lesions persist and transmute into a well recognized entity. It is well to bear in mind that this eruption lasts for many years as an innocent disease and then develops into a lymphoblastoma. The disease in this case has some of the early earmarks of mycosis fungoides.

DR. E. W. ABRAMOWITZ: I do not recall any case of erythema annulare centrifugum that turned out to be mycosis fungoides. My patients responded to intramuscular injections of a bismuth preparation, but cure is not permanent.

DR. BEATRICE M. KESTEN: I have never cured one of these patients, but I have never tried a bismuth preparation. I think that histologic examination would differentiate erythema annulare centrifugum from mycosis fungoides d'emblée.

DR. DAVID BLOOM: This patient was treated at the Skin and Cancer Clinic with injections of bismuth compound and benefited greatly, although some lesions have reappeared. The diagnosis of erythema annulare centrifugum was made. This belongs to the large category of erythema multiforme. In the persistent type of the disease, bismuth compound has proved more effective in my experience than any other remedy.

DR. ANDREW H. MONTGOMERY: I am sorry that this patient could not have been shown six weeks ago. I have gone through the literature of the last ten or twelve years rather carefully, and there has been no mention of the development of lymphoblastoma of any sort. To quote Dr. Michelson, "There are many forms of this disease, and very little is known about it."

Generalized Dermatomycosis (Trichophyton Purpureum) Associated with Hyperkeratosis Palmaris et Plantaris. Presented by DR. RUDOLF L. BAER and DR. EMANUEL MUSKATBLIT.

A. R., a man aged 25, was previously presented before this section on Feb. 1, 1944, with a diagnosis of erythroderma ichthyosiforme congenitale (ARCH. DERMAT. & SYPH. **51**:161, 1945). He has had an eruption on the hands and feet since birth and on the body since the age of 13 or 14. He stated that he did not perspire except on the face and scalp. The p_H of the skin of the face and ear area varied between 4.2 and 4.5 and of the rest of the body between 4.3 and 6.5, with the majority of values lying between 5.0 and 6.0.

With treatment with pragmatar,® containing coal tar distillate, colloidal sulfur and salicylic acid, almost the entire eruption cleared. The patient stated that he notices some perspiration on the body. He now presents palmar and plantar hyperkeratosis and on the legs several well defined slightly scaly patches with a somewhat raised border. The finger nails are yellowish (they are regularly scraped down by the patient). The toe nails show the same discoloration and onychogryphosis. (This case has been published in detail in ARCH. DERMAT. & SYPH. **56**:834, 1947.)

DISCUSSION

DR. DAVID BLOOM: When observed at the Skin and Cancer Clinic a few years ago, this patient did not present the well defined scaly plaques shown on the photographs here. He showed thickened reddened hyperkeratotic skin on the abdomen, lower part of the back, knees and wrists, with keratosis palmaris et plantaris. At that time this disease, which has been present since early childhood, was diagnosed as congenital erythroderma ichthyosiforme, in which group it fitted best. The mycotic infection which has developed was unquestionably superimposed on the original disease.

DR. ROYAL M. MONTGOMERY: The presenter has had an excellent result so far in this patient. Lesions on the glabrous skin caused by Trichophyton purpureum respond much more quickly than those on the palms and soles. Any strong fungicidal remedy will clear up the glabrous skin. However, the hands and feet present a more difficult problem and it takes persistent treatment to effect any permanent improvement.

DR. E. W. ABRAMOWITZ: I am sure that most of us who saw this patient at the clinic agreed that he presented a classic picture of erythroderma ichthyosiforme. The photographs presented tonight of the lesions on the body certainly do not give the impression of ichthyosis of any type. It is possible that a secondary fungous infection developed, but it is strange that Dr. Muskatblit could not grow this organism after so many attempts.

The palmar and plantar lesions seen now do not give the impression of onychomycosis, but rather of a dystrophy, with keratosis of the palms and soles.

DR. JESSE A. TOLMACH: I have seen only a few generalized T. purpureum infections of the skin. They are not common. Though the disease responds to local applications of benzoic and salicylic acid ointment or weak tincture of iodine, there are usually recurrences.

DR. RUDOLF L. BAER: I agree with Dr. Goodman that this patient is suffering from two diseases, namely, a nevoid anomaly and a generalized fungous infection. We believe that the nevoid anomaly makes this patient susceptible to the fungous infection. We do not think there can be any doubt that this patient had a generalized fungous infection in view of the characteristic fungous mycelia found in almost all the scrapings taken from many different areas. The patient stated that two days after starting to use a tar-sulfur-salicylic acid preparation the eruption began to disappear. From histologic examination of tissue from the back the disease was diagnosed in 1944 as characteristic of erythroderma ichthyosiforme congenitale, although that diagnosis was not upheld by our own observations at any time. The man undoubtedly has a nevoid anomaly, and our assumption is that the tendency of this patient to have a generalized infection with T. purpureum is due to this congenital anomaly. The patient stated that he never perspired below the neck up to the time the eruption disappeared; since then he has begun to perspire in the armpits and on the chest. We expect to study the patient's

sweat output to see whether there is any objective evidence of an anomaly of the sweat mechanism.

DR. EMANUEL MUSKATBLIT: I believe that this case is interesting from several points of view. First of all, it is a generalized dermatomycosis. Large areas of the trunk and extremities were formerly affected. Now there is no eruption on the trunk and only a little involvement of the right leg, but both hands and feet and all finger nails and toe nails are still affected. Dr. Baer obtained cultures from a lesion on the neck which showed T. purpureum. I saw the patient later and took several scrapings from the wrists, palms, thighs, toes, soles, finger nails and toe nails. All specimens contained fungi of the pathogenic type in microscopic preparations. Cultures were made in twenty-one tubes, and all were overgrown with saprophytic organisms, so that we were unable to obtain the pathogenic species. I believe with Dr. Baer that the erythematosquamous lesions and the changes of the finger nails and toe nails are due to a fungous infection which developed on the basis of a preexisting anomaly of the skin, though what the relationship is would be difficult to say. Ichthyotic skin presents a mass of scales on the surface which may be a good soil for the propagation of fungi. On the other hand, the dry skin is unfavorable for the growth of fungi, but the lack of sweat with its chemical substances inhibiting the fungi is again favorable for their propagation. It is worth while mentioning that we did not obtain cultures of T. purpureum from all lesions. We assume, however, that all the lesions we have seen and see now are at least partially due to fungous infection, in this instance T. purpureum. This is considered a highly resistant fungus, but the eruption on the trunk has cleared up in a short time, so that it seems that not all cases of T. purpureum infection are as resistant as some reports would have one believe.

Tuberculosis Colliquativa of the Ankle. Presented by DR. S. IRGANG.

Dermatitis Medicamentosa (Atabrine), Lichen Planus, Atrophy, Scars, Alopecia, Pigmentation, Nail Changes. Presented by DR. ANDREW H. MONTGOMERY.

Lymphangioma Circumscriptum of the Knee, Thigh and Abdominal Wall. Presented by DR. S. IRGANG.

Herman Sharlit, M.D., *Chairman*

Maurice J. Costello, M.D., *Secretary*

Oct. 1, 1946

Micropapular Tuberculid. Presented by DR. S. IRGANG.

Tuberculosis Miliaris Disseminata Faciei. Presented by DR. S. IRGANG.

DISCUSSION

DR. SAMUEL IRGANG: Negroes are generally more sensitive to tuberculin than are white patients. In this disease the Negro usually reacts locally to an intracutaneous injection of 0.1 cc. of old tuberculin in a dilution of 1:1,000, and positive reactions with a dilution of 1:10,000 are not unusual. The lesions of tuberculosis

miliaris disseminata faciei heal with great difficulty in the Negro. I have not seen the eruption resolve entirely in any case, even after a year or more of observation.

Multiple Tuberculids; Lichen Scrofulosorum Now Present. Presented by Dr. Louis Tulipan.

DISCUSSION

Dr. Marion B. Sulzberger: We all know that the tuberculoderms, in all their various forms and combinations, are much commoner in the Negro than in the white population and that, in particular, the transitional forms between the different kinds of tuberculoderms, including lupus, tuberculids and sarcoids, as well as tuberculosis of the soft parts, are commoner in the Negro. I should like to call attention to the most successful measures of treatment of lupus vulgaris and scrofuloderma introduced by Charpy in France in 1941, which were first published in 1943. Charpy's results were simultaneously and independently confirmed by the studies of Dowling and his co-workers in England. These measures consist of the administration of large doses of vitamin D_2 by mouth, plus a supplement of small doses of calcium salts by mouth or simply milk by mouth. According to reports, this treatment has radically improved the prognosis in many cases of severe lupus vulgaris: 80 or 90 per cent of the lesions disappear with this treatment. This therapeutic approach and its results perhaps throw some light on why there is more tuberculosis among Negroes than among white persons, because, of course, the vitamin D formation in the average Negro skin is likely to be less than in the white. Moreover, the diet of the Negro is often apt to be lower in vitamin D-containing foods and calcium, so that perhaps the success of this form of therapy and the higher incidence of cutaneous tuberculosis and the many diverse forms of tuberculosis in the Negro are related. I should like also to call attention to the theory (as already pointed out by both French and English schools) that older and more difficult dietary forms of treatment for tuberculosis, namely, salt-poor diets and vitamin additions as suggested by Gerson, Hermannsdorfer and Sauerbruch, are effective actually because of the large amounts of calcium and vitamin D_2 which they contain. It seems to me that this new therapy may be a superior and more sharply focused method of accomplishing the same effects. At any rate, the Charpy-Dowling method is well worth trying in all forms of cutaneous tuberculosis and in tuberculosis of the subcutaneous structures and of certain viscera. I hope that it may also find some use in selected nontuberculous diseases.

Dr. Samuel Irgang: I was under the impression that the greater frequency of tuberculids in the Negro was due to the higher incidence of tuberculous disease associated with lowered resistance. Its relation to a deficiency of vitamin D_2 in the skin is most interesting.

Dr. Louis Tulipan: The interesting thing about this patient is the fact that he had various manifestations of his tuberculosis on the skin. He had previously had erythema induratum, which had healed, then papulonecrotic tuberculids, the scars of which he shows on the extremities. Recently lichen scrofulosorum developed. A week ago there developed tiny white, shiny, discrete papules closely aggregated on the side of his neck, which fit well into the picture of lichen nitidus. It is certainly interesting that in one patient there may be found these various manifestations of the disease.

A Case for Diagnosis (Mycosis Fungoides? Dermatitis Herpetiformis?). Presented by Dr. Frank C. Combes.

Dermatitis Medicamentosa (Phenolphthalein) Followed by Pigmentary Changes. Presented by DR. FRANK VERO.

L. S., a Negro aged 37, is presented from the New York Polyclinic Medical School and Hospital with an eruption of five months' duration, located on the lips, perioral region and left wrist.

The patient was seen for the first time on Aug. 27, 1946, complaining of a recurrent eruption on the lips and wrist of four months' duration. When questioned as to intake of drugs, he said that he had changed from salt cathartics to ex-lax® (a laxative containing phenolphthalein) within recent months. There were no pigmentary changes on the lips prior to the appearance of the eruption.

The upper and especially the lower lip appeared swollen, with numerous vesicular and bullous lesions and oozing denudations and covered with yellowish and hemorrhagic heaped-up crusts extending to the perioral region. The tongue and buccal mucosa were clear. Over the flexor aspect of the left wrist there was a half-dollar-sized, sharply outlined, reddish brown edematous lesion. On the neck, chest and abdomen were scattered round and oval dark, pigmented and scaly lesions (typical pityriasis versicolor). The Wassermann and Kahn reactions of the blood were negative. A week later, following treatment with penicillin ointment, the eruption on the lips and wrist cleared up except for the pigmentary changes. On September 12, three days after the intake of 2 tablets of ex-lax,® the patient had an exacerbation in the form of vesicles and bullae. He stated that ten minutes after he took the drug his lips became swollen and blistered. At present the lips show depigmentation, more so on the lower lip, and hyperpigmentation, the latter extending to the perioral region in a semicircular outline, with similar pigmentary changes on the left wrist.

DISCUSSION

DR. MARION B. SULZBERGER: Cases of phenolphthalein eruption are beginning to belong to the rarities in clinics or offices. Most patients now know, or find out before they come to the skin specialist, that it is phenolphthalein which has caused their eruption and simply stop taking the drug. This is in contrast to the situation years ago when such eruptions were first described and the public and general medical profession were not as aware of the possibility of eruption from this cause. I think that many of the younger men here may have seen few if any of such fixed eruptions from phenolphthalein. I think that this case is instructive as to what an inflammatory process can do in the way of disturbing the pigment formation. I am sure that it is not unusual for long-lasting hyperpigmentation to form as a result of certain kinds of inflammation; and the nature of the inflammatory process, its location, its mechanism and cause all have something to do with the degree and persistence of resulting pigmentation. Fixed eruptions due to phenolphthalein and those from certain other drugs have a strong tendency to leave long-lasting hyperpigmentation. One sees that illustrated in this case, and that is not the unusual feature. On the other hand, I do not recall having seen a case of fixed eruption which has left the patchy permanent (or probably permanent) destruction of pigment which is evident here. I should like to ask Dr. Abramowitz and others whether they have seen such cases.

DR. E. W. ABRAMOWITZ: At an exhibit of the American Medical Association I showed a photograph of a patient who presented a patch almost the size of the palm and located below the left scapula with a form of the stippled pigmentation which Dr. Vero's patient shows. He had had several outbreaks, and apparently the pigment reacted in this particular way. These cases are unusual, though several

have been described. I have not seen the eruption around the mouth, affecting the vermilion surface and the skin below it. If the patient is not exposed to the drug again, the pigmentation resumes a normal appearance in time.

The other question raised by Dr. Vero was whether it is correct to call this type of reaction a fixed eruption. I think that it is correct, because the term fixed eruption refers to any cutaneous manifestation that may appear as long as the eruption recurs at the exact site of a previously affected area. This patient took 2 tablets of a preparation which contains a mixture of the yellow and white forms of phenolphthalein. It would not matter whether he took the yellow or white variety of the drug, as either would cause an exacerbation. He should be questioned as to whether he is taking barbiturates or any other of the fourteen or fifteen drugs capable of producing fixed eruptions. The patient may experience sensitivity to other drugs, such as the barbiturates or, as in one interesting case, to magnesium hydroxide.

DR. FRANK VERO: I thought that the pigmentary changes, and especially the depigmentation, were rather unusual. When first seen the patient presented a clinical picture of herpes labialis or an actinic dermatitis possibly secondarily infected. He denied exposure to sunlight but admitted having taken ex-lax® as a cathartic. I was hesitant to diagnose the disease in this case as a fixed eruption because of the inflammatory changes which preceded the pigmentation and depigmentation. I am glad to be enlightened by Dr. Abramowitz that eruptions of this type can be considered as fixed eruptions, although at many of our section meetings somewhat different views have been expressed by experienced dermatologists. I should like to add that the exacerbation which the patient presented tonight on the wrist appeared after the ingestion of 2 tablets of ex-lax® (a laxative containing phenolphthalein) this morning.

Boeck's Lichenoid Sarcoid; Iridocyclitis; Ptosis. Presented by DR. MAURICE J. COSTELLO.

L. R., a Negro aged 24, is presented from Bellevue Hospital with a generalized eruption. The patient was well until nine months ago, at which time there developed an eruption of the legs, which gradually spread to involve the whole body. About the time the eruption appeared, the patient had a "cold," which has persisted to date. There was no pruritus until two weeks ago, when itching became intense. Three months after the appearance of the eruption the patient experienced iridocyclitis of the left eye, for which he received penicillin at another institution. He has lost 30 pounds (14 Kg.) in the past year.

The lesions, consisting of papules and plaques, violaceous to brown and infiltrated but freely movable in the skin, are present on the extremities, face and trunk. There is generalized adenopathy; the spleen is palpable 3 fingerbreadths below the costal margin; the right testis is atrophic, and there are changes in the left eye compatible with iridocyclitis. Respiratory excursions are limited on both sides, but particularly on the left.

The red blood cell count was 4,130,000, with hemoglobin 13 Gm. per hundred cubic centimeters; the white blood cell count was 7,650, with 61 per cent polymorphonuclear leukocytes, 7 stab forms, 31 lymphocytes, 2 monocytes, 2 eosinophils and 1 basophil. The urine was normal. The total protein in the blood was 8.1 Gm., with albumin 3.1 and globulin 5.0 Gm. The cephalin flocculation result was 4 plus, the icteric index 8.8, cholesterol 154 mg., nonprotein nitrogen 28 mg. per hundred cubic centimeters, sugar normal, chlorides 500 mg. per hundred cubic centimeters and vitamin C 0.58 mg. per hundred cubic centimeters. The result of the Mazzini

test was negative. The erythrocyte sedimentation rate was 23 mm. per hour. The skin did not react to 1.0 mg. of old tuberculin. Roentgenographic examination of the chest showed numerous miliary pea-sized nodules uniformly distributed over both lung fields, compatible with the diagnosis of Boeck's sarcoid. Results of roentgenographic examination of the bones were normal. Histologic examination of a cutaneous lesion showed numerous tubercles composed of epithelioid cells, located within the corium, chiefly about the hair follicles and sweat glands. Multinucleated giant cells were present in a few of these tubercles. In one rare tubercle there was early necrosis. Acid-fast stain failed to demonstrate acid-fast bacilli. The diagnosis by Dr. W. C. Von Glahn was "granulomatous lesion—either tuberculosis or Boeck's sarcoid, possibly the latter."

DISCUSSION

DR. DAVID BLOOM: This case represents the so-called hematogenous tuberculosis of the skin in the Negro. The prognosis in this case is much better than one would think, considering the extent of the eruption and the involvement of the viscera. One of the cases which Dr. Mendelsohn and I reported about ten years ago was presented a few years ago at the New York Academy of Medicine; the disease cleared up entirely without any particular treatment.

DR. LOUIS CHARGIN: I agree with the diagnosis. I should like to urge an extensive trial of the Kveim test to determine whether it really has merit in the diagnosis of sarcoidosis. This test is similar to the Frei test. The material for the test is prepared from cutaneous lesions or affected tonsils or glands of patients with sarcoid in exactly the same way as material for the Frei test. Considerable work has been done with this test in Europe, and there are a number of favorable reports. I think that it should be given an extensive trial in this country.

DR. FREDERICK REISS: In connection with Dr. Chargin's remarks about the Kveim test, the literature is already extensive in the Scandinavian countries. Kreim published a monograph in which he stated that in 80 or 90 per cent of cases there are specific reactions. I believe that it is an important test, not only in the diagnosis of sarcoid but with respect particularly to the conflict which exists among South American dermatologists regarding the relationship of sarcoid to leprosy. There is a good deal of similarity in the histologic pictures, and therefore a group of South American leprologists tried to link leprosy with Boeck's sarcoid. The Kveim test definitely eliminates the controversy. I think that it would be interesting to try the Kveim test in leprosy as well.

DR. FRANK VERO: Several years ago similar cutaneous tests in sarcoid were carried out by two Boston men in a limited number of cases (Williams, R. H., and Nickerson, D. A.: Skin Reactions in Sarcoid, *Proc. Soc. Exper. Biol. & Med.* **33**: 403 [Dec.] 1935). The material used was tissue taken from sarcoid lesions and prepared as is the Frei antigen.

DR. MAURICE J. COSTELLO: Nickerson made an antigen from sarcoid nodules which when injected intradermally produced reactions in the skin similar to those obtained with the tuberculin test.

When this patient was first presented at conference at Bellevue Hospital, the eruption suggested generalized lichen planus, especially since it was accompanied with severe itching. I think that this patient has lichenoid sarcoid. For a number of years the patient received arsphenamine therapy for syphilis.

I had the impression that the arsenic therapy precipitated this eruption. It seems to me that this patient may also have beginning active pulmonary tuberculosis, because of the productive cough, although roentgenograms of the chest suggest

miliary sarcoidosis. It is difficult to differentiate among sarcoidosis, pneumonoconiosis, acute miliary tuberculosis and carcinomatosis in roentgenograms of the chest.

A Case for Diagnosis (Dermatitis Medicamentosa?). Presented by DR. LOUIS TULIPAN.

P. C., a woman aged 60, born in Russia, is presented from Bellevue Hospital with an eruption on the left leg of two years' duration. The patient presents two quarter-sized bullae arising from normal skin on the anterior aspect of the lower third of the left tibial region. There are small erythematous papules surrounding the bullae. The bullae are turbid and almost solid in character and do not exude fluid when punctured with a needle. The lesions were first noticed in June 1944, after a pruritic papular eruption in that area. The lesions disappear sporadically, only to recur. They are clear when they first appear, but become cloudy after a few days.

The patient's past history and family history are irrelevant.

In June 1946, she was hospitalized. She was found to be sensitive to soap, plaster and sunlight. A culture of the bullae contents in April 1946 grew gram-positive rods, and the smear showed 24 per cent eosinophils. The urine has always been normal. Culture of bullae contents in June 1946 grew Staphylococcus aureus and diphtheroids. A smear of the contents September 30 showed no cells. The results of a complete blood cell count were normal.

DISCUSSION

DR. E. W. ABRAMOWITZ: I am sure that if the patient gave a history of having taken bromides Dr. Tulipan would consider the eruption a bromoderma. I think that she presents a bromoderma, as her denial of medication is too vehement. It is possible that she is getting the bromide or iodide in some other form, as in food. I would wait until the lesions subside and then watch for a recurrence with a test dose of a bromide or iodide.

DR. ISADORE ROSEN: Another possibility which must be taken into consideration is that of contact dermatitis. Occasionally one sees patients who experience local reactions of a vesicular and bullous nature due to shoe dyes.

DR. LOUIS CHARGIN: I would agree with the diagnosis of bromoderma if a history of the ingestion of the drug could be obtained. Is it pertinent to ask whether bromides produce fixed eruptions? The process may be an artefact, and its persistence in the same spot would favor an artefact as against bromoderma.

DR. FRANK C. COMBES: When one sees a bizarre eruption for which one cannot give a definite diagnosis, it is always customary to consider an artefact or an eruption due to drugs, and I think that one or the other is the most likely diagnosis here. I favor an eruption due to drugs, and I agree entirely with Dr. Abramowitz. There are two types of eruptions due to the halogens: one due to their cumulative effect and the other to sensitivity. Sensitivities due to the halogens are unusual and may be serious. Fatalities have been reported. The tendency in this case for the eruption to recur in a fixed location without any history of ingestion of bromides is evidence in favor of an unusual sensitivity to bromides, and I also agree with Dr. Abramowitz that the only real test would be the administration of bromides. One cannot determine by ordinary tests or blood estimations whether an eruption is due to bromides, because cutaneous and even nervous lesions due to bromides are not necessarily dependent on the amount present. A patient may have a large amount of bromides in his system without any evidence of bromism, whereas in other instances an infinitesimal quantity will produce symptoms. I feel that the

most likely diagnosis in this case is that of bromoderma, but there are certain elements about it which make me hesitate to make any definite decision.

DR. HERMAN SHARLIT: Has anyone attempted topical application of bromine salt?

DR. E. W. ABRAMOWITZ: I do not exactly agree with what Dr. Combes said. Psychiatric studies of patients admitted to mental hospitals who have been taking bromides indicate that their mental symptoms are due to long-continued use of bromides. It is only when the bromide content reaches 75 mg. or more per hundred cubic centimeters of serum or spinal fluid that mental bromism takes place. There are patients who show a high amount of bromides in the tissue fluids who still do not show mental bromism, but the fact remains that the patients who do present mental bromism or iodism all show large amounts of those drugs in the blood. The majority of patients who show mental bromism or iodism do not have cutaneous lesions. Only about 20 to 25 per cent present eruptions, and they are of a comparatively minor type. Apparently those patients who get cutaneous eruptions from bromides or iodides do so because of sensitivity and not from accumulation. As a rule those patients do not present mental symptoms. I recall only one patient, an epileptic patient who took bromides, who had an extensive cutaneous eruption, and the blood serum and spinal fluid showed large amounts of bromides. That brings up the important question of salt therapy. I do not believe that one should fear giving salt to patients with bromoderma or iododermas, but one should be careful when there is a large amount in the blood of patients with mental symptoms, because to further release of bromides or iodide is apt to have serious results.

DR. ISADORE ROSEN: I should like to ask the presenter when the patient had a previous attack.

DR. LOUIS TULIPAN: In June. She was entirely well during the summer; new bullae developed two or three weeks ago.

DR. ISADORE ROSEN: That is unusual with bromides. The eruption usually persists for months. I do not recall having seen this type of eruption from bromides. Usually one sees nodular lesions which may ulcerate.

DR. FRANK C. COMBES: I agree with Dr. Abramowitz; I did not mean to imply that mental bromism was a manifestation of sensitivity to bromides. I still feel, however, that in bromism there are cutaneous symptoms which represent either sensitivity or accumulation of the drug. I have observed patients with bromism who have been given sodium chloride to aid elimination of bromides, and further administration of bromides was not accompanied with exacerbation immediately, but only after the bromides had again accumulated. As to Dr. Rosen's remarks, I agree with him entirely that the remissions and relapses in this patient are an unusual feature. It is extremely unusual for bromoderma of the granulomatous type to disappear spontaneously. The lesions will persist for months, long after administration of the bromide has been discontinued. In fact, this is the feature in this case that makes me doubt the diagnosis of bromoderma.

DR. LOUIS CHARGIN: It is my impression that eruptions due to bromides are observed only as cumulative phenomena, the threshold varying so that either larger or smaller doses are required to bring out an eruption. However, minute doses do not cause eruptions, as in the case of drugs that act as allergens. In the case of iodides, however, a minute dose may produce an eruption and, also, the eruption may be a cumulative phenomenon.

DR. MAURICE J. COSTELLO: Eruptions due to bromides which occur on the lower anterior third of the leg are always painful, are fixed and not evanescent and are the result of accumulation of the drug in the system. Bullous eruptions

are rare following bromide ingestion. I think that this is an eruption due to drugs but not caused by bromides. The evanescence of the eruption and frequent recurrence do not favor a diagnosis of fixed eruption due to the bromides.

DR. LOUIS TULIPAN: This discussion is a repetition of that at the clinic, and we are still in the dark. I saw the patient almost every time these bullae developed; they all contained clear fluid at first, springing right off the skin without any erythema at the border, as do bullous eruptions seen in pemphigus. Within a few days they become pustules. I could not get a history of ingestion of drugs, which was the first thing I thought of when I saw the patient. Because she was seen in summer I thought of hydroa estivale, but then bullae developed in winter, and tests were made with applications of coal tar and exposure to the sun lamp, with no reaction. The patient absolutely denies having taken drugs, and there is no reason for her to do so. I also thought that it might be bullous impetigo, but against that was the fact that the capsule was intact and remained intact for so long, and the bullae in impetigo rupture quickly. These bullae have been present for three weeks; I purposely did not evacuate them as I wanted to present the patient. As far as dermatitis factitia is concerned, I do not believe that it could account for the eruption, because the lesions are so well circumscribed. The case is one of those in which I simply cannot make a diagnosis.

Livedo Reticularis with Ulcerations. Presented by DR. MAURICE J. COSTELLO.

PHILADELPHIA DERMATOLOGICAL SOCIETY

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May 17, 1946

Dementia Paralytica. Presented by DR. JOHN H. STOKES and DR. HOWARD P. STEIGER (by invitation).

R. R., a white man aged 54 years, has dementia paralytica, with unequal pupils, bilateral ataxia, poor handwriting, pronounced euphoria and slurred speech. He is unable to concentrate and has epigastric pain and ataxia of one years' duration. He had received three injections of an arsenical and four of a bismuth preparation prior to admission.

From Feb. 1 to Feb. 24, 1944, he received 2,400,000 units of sodium penicillin. His mental state and speech are now normal.

Results of Tests

Date	Days	Wassermann Reaction of the Blood	Cerebrospinal Fluid			
			Cells	Protein	Wassermann Reaction	Results of Mastic Test
2/15/44	0	32 units	10	75	4444	4555543110
3/15/44	20	32 units	4	50	4444	3455542100
4/25/44	61	32 units	6	30	4444	4555321100
5/31/44	127	64 units	0	20	0011	0111100000
7/ 5/44	162	4 units	8	40	1244	2444311000
9/26/44	216	Doubtful	4	20	0133	2221100000
1/30/45	342	8 units	1	20	0000	1111100000
5/ 1/45	433	Negative	1	20	0000	1111100000
10/31/45	614	32 units	0	20	0000	1111000000
2/20/46	726	16 units	1	40	0000	1111000000
5/ 8/46	825	64 units	0	10	0000	0111000000

Taboparesis (Treated). Presented by DR. JOHN H. STOKES and DR. HOWARD P. STEIGER (by invitation).

R. K., a white woman aged 49 years, with no history of genital lesions or previous antisyphilitic therapy, presents pronounced disorientation of six to eight months' duration. She is unable to carry on household duties. She was first seen in February 1944, at which time she showed decided disorientation, slurred speech, ptosis of the left eyelid, fixed pupils and absent knee and ankle jerks. The electroencephalogram showed no abnormalities.

From March 3 to March 17, she received 3,000,000 units of sodium penicillin. From April 20 to April 28, 1945, she received 2,400,000 units of sodium penicillin with considerable clinical improvement during the two months following the first course of penicillin. She has maintained this improvement.

DISCUSSION

DR. ISADORE ZUGERMAN: Was there a Herxheimer reaction when the treatment with penicillin was started?

DR. HOWARD STEIGER (by invitation): Treatment of both patients was begun with only 10,000 units every three hours, and each had a slight temperature elevation, the first to 100.4 F. and the other to 101 F. They had no other manifestations.

DR. JOHN H. STOKES: In relation to the small amount of penicillin which it takes to do a large amount of good, the effect of penicillin is not unlike that of malaria. A single course of penicillin goes on working for months or even years after it has been administered. You are all aware of the qualifications in the current statements about the therapeutic effects of penicillin. We have the penicillins and the proportions of the F, X, G, and K fractions. This patient was treated in the days when we assumed that penicillin had a good deal of the impurities which almost certainly contain antisyphilitic products not included in the high potency penicillin. We must, therefore, first attempt to find those things which are antisyphilitic in their effects and then put them into our present preparations and determine whether any of the crystalline preparations have as much effect as the old, low unit, impure penicillin with which good results had been obtained. I do not have the impression that there has been such a decline in the efficacy of commercial penicillin as some doctors would lead one to think had occurred, so I am less alarmed about the ultimate future of penicillin. I think that a six months' program of modifications of cultural methods and the selection of somewhat better strains will iron things out. These patients illustrate how much the older penicillin accomplished with a smaller dose in a shorter time.

Lupus Erythematosus, Subacute, at Age 70. Presented by DR. DONALD M. PILLSBURY and DR. LAWRENCE KATZENSTEIN (by invitation).

DISCUSSION

DR. DONALD M. PILLSBURY: This is our best result so far with bistrimate® (sodium bismuth triglycollamate). We had been rather disappointed on the whole, but this patient has certainly shown a decided improvement. I think that it is of some interest that the disease developed in this patient at the age of 70 years.

A Case for Diagnosis and Therapeutic Suggestions. Presented by DR. JOHN H. STOKES and DR. STEPHEN T. WHELAN (by invitation).

V. H., a white woman aged 40 years, presents at the right angle of the mouth a dry, slightly atrophic, slightly scaling, circular patch which occasionally has some papules and pustules. On the chin below the mouth there is a similar superficial

erythematous scaling and fissuring circular patch. In November 1939, the patient noted an erythematous circular patch at the corner of the mouth which steadily grew, so that in one month it involved the entire chin and the area around the mouth and was eczematous. Lesions have persisted at the left angle of the mouth and the right side of the chin, with a tendency to fissuring.

Patch tests with cosmetics resulted negatively. Results of various patch tests with feathers, grasses and animal hair were also negative. Positive reactions were obtained with scratch and intradermal tests of the following substances: camel hair, chicken feathers, duck feathers, goose feathers, goat dander, orris root, stock house dust, autogenous house dust, sheep wool, silk and cow and dog dander. The result in an intradermal test with tobacco was moderately positive, but the reaction to the scratch test was negative. The patient had a number of positive reactions to foods.

She has been given injections of ambotoxoid for desensitization purposes and has received treatment with castellani's paint; 0.5 per cent ammoniated mercury in boric acid ointment, ten injections of colloidal manganese hydroxide, penicillin ointment (with some improvement), boiled milk given intramuscularly (five times), injections of 5 cc. of Upjohn's solu-B® (in sterile powder vials, each containing 10 mg. thiamine hydrochloride, 10 mg. riboflavin, 5 mg. pyridoxine hydrochloride, 50 mg. calcium pantothenate and 250 mg. nicotinamide) three times a week for twelve weeks, with no change.

DISCUSSION

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I think that the patient has a discoid type of lupus erythematosus.

DR. J. V. KLAUDER: I could not make much of the eruption except that it was an eczematous type of dermatitis. She has an introspective, self-analytic attitude toward the lesion. I thought that there was some excoriation present. There was a white area which I was not sure was atrophy. It suggested some manipulation I do not mean dermatitis factitia, but perhaps a nervous picking or manipulation of the lesion, causing it to persist.

DR. JOHN H. STOKES: Years ago Pusey described in his textbook what he called resistant scaly erythrodermias of the skin, and in the last three or four years I have seen 4 or 5 cases of this disease. The lesion was a refractory erosive plaque of dermatitis which simply responded to nothing. A common location is around the edge of the scalp, but lesions occurred around the chin and at the angles of the mouth. I saw such cases at the Mayo Clinic, and 4 or 5 in Philadelphia. They are *sui generis*. This woman has certain attributes of the person who presents a factitial eruption—perhaps unconsciously. I was glad to hear Dr. Klauder speak as he did about her attitude—the almost exhibitionistic eagerness to show the lesion and cooperate in every imaginable way. She is a divorcee with a very considerable tension problem, and I think that she probably picks the lesion in her sleep. On the other hand, she has pustules, which lead me to think that the process might be staphylodermic and represents one of the localized pyogen-sensitive areas which just go on producing localized infections until the whole thing becomes a fibrous inflammatory plaque. Pusey's cases responded finally to one thing—treatment with Kromayer lamp—and we are now treating her with the air-cooled quartz lamp using a quartz lens. Since that was started she has made a good deal of progress. She has, however, improved with nearly everything that has been done for her, for a while. The scarlike atrophy exhibited today is new. The lack of elevation is also new. The lesion had been so elevated that it looked almost like a granuloma. She is a little paranoid, and one hesitates to take even a punch biopsy specimen from her

face. The fissure on the chin is a favorite staphylococcic location in certain types of persons who have lesions there for years and years, after every other focus has been cleared up. I favor a diagnosis of resistant staphylodermia, or resistant scaly erythroderma as it was called by the older dermatologists. We have included vitamins to exclude vitamin B_2 deficiency, and we have found no tuberculosis.

Lupus Vulgaris. Presented by DR. DONALD M. PILLSBURY, DR. CLARENCE S. LIVINGOOD and (by invitation) DR. JOHN P. SCULLY.

A Case for Diagnosis (Histiocytoma Cutis? Calcified Cyst? Nodular Subepidermal Fibrosis?). Presented by DR. REUBEN FRIEDMAN.

(NOTE: The histologic diagnosis of the mass from the left shoulder was: "Intracystic papilloma [hard] of duct of pilosebaceous apparatus.")

Reticulosis. Presented by DR. JOHN W. LENTZ and (by invitation) DR. MALCOLM SPENCER.

E. S., a Negro man aged 61 years, normally developed and fairly well nourished, presents residual, hyperpigmented, annular, slightly infiltrated, finely scaling plaques, the residuals of his original lesions. Physical examination revealed generalized shotty adenopathy. The cardiovascular, gastrointestinal, genitourinary and urologic examinations revealed no abnormalities.

A complete blood cell count on Feb. 13, 1946, showed 63 per cent hemoglobin, 3,100,000 erythrocytes, 4,100 leukocytes, 54 per cent neutrophils, 2 per cent eosinophils, 2 per cent monocytes and 42 per cent lymphocytes. The blood sugar level and results of urinalysis were within normal limits. The results of serologic tests of the blood for syphilis were negative. Gastric analysis revealed no free hydrochloric acid. A roentgenogram of the chest and a biopsy specimen of bone marrow showed no abnormalities.

From a biopsy specimen of the skin taken on February 18 the diagnosis was "leukosis-mycosis fungoides (??)" and from a biopsy specimen of a left axillary lymph node on February 20 "reticulum cell hyperplasia."

Treatment was with roentgen rays, through thirty-five portals, total dosage varying from 300 to 1,200 r, 135 kilovolts through a 2 mm. aluminum filter. The individual dosage was 100 to 400 r. Improvement was striking.

DISCUSSION

DR. HERMAN BEERMAN: This patient has been presented on two previous occasions, originally with the diagnosis of psoriasis and the second time with the diagnosis of mycosis fungoides. I could not reconcile the diagnosis of mycosis fungoides with the histologic sections. I took the sections to Dr. Weidman, who made the diagnosis of reticulosis.

DR. FRED WEIDMAN: In a loose way, one can say that "reticulosis" is a way of getting out of the histologic diagnosis of granuloma fungoides. Clinically it may be just that, and yet histologically it is not satisfactory; there is not the polymorphism of cells that one reads about in the textbooks. It is hyperplasia of the reticulum and nothing else—no plasma cells and no eosinophils. This serves to illustrate that there are numerous upsets of the hematopoietic system that have not been classified in the dermatologic nomenclature. Every now and then one is driven to some such recourse as "reticulosis." The processes do not fit any of the accepted pigeonholes in dermatologic nomenclature, and one must give it a histologic diagnosis.

DR. HERMAN BEERMAN: This whole subject is very ably presented in the *British Journal of Dermatology* by a number of men, including Goldsmith and Robb Smith (**56**:107, 1944 and **56**:151, 1944, respectively).

Contact Dermatitis with Probable Food Sensitivity. Presented (by invitation) by DR. JAMES M. FLOOD and DR. MALCOLM C. SPENCER.

R. N., a white woman aged 39 years, obese and normally developed, presents residua of deep seated vesicles with some evidence of pyoderma, since one week ago, on both heels. The condition had its onset in August 1944, while the patient was on vacation. Red scaling pruritic plaques developed on both heels. The patient was wearing a pair of new shoes at the time. Also a small plaque of lichenification developed on the dorsa of both feet. There have been recurrent vesicles since the onset of the condition. Eating tomatoes has caused "hives." Drinking one glass of beer causes rhinitis.

A blood cell count on April 8, 1946, revealed 72 per cent hemoglobin and 7,800 leukocytes. A urinalysis resulted negatively. Serologic tests of the blood for syphilis resulted negatively. The serum protein and cholesterol were 6.5 Gm. and 223 mg., respectively, per hundred cubic centimeters of blood. The basal metabolic rate was —7 per cent.

Culture for fungi produced no growth. Patch tests with several different kinds of shoe leather gave positive reactions. An injection of trichophytin, 1:100, yielded a positive reaction.

The patient was given a trial diet plus the use locally of bland ointments. Flare up occurred with the ingestion of beef, tomatoes, egg, cream of wheat and corn. In our practice, trial diets are instituted after a period of two to three days' hospitalization during which time the patient is observed frequently and a base time of improvement or progression is reached. During the first twenty-four hour period the patient receives nothing but water and dextrose, followed by the addition of one simple food daily. In the case of this patient, after the addition of beef, which was the third day of her trial diet, there occurred a few vesicles on the soles as well as on the great toes. These were interpreted as representing a flare up. Within forty-eight hours it was possible to add a new food, and this was continued until tomatoes were introduced into her diet, which produced an urticaria-like reaction on the arms as well as the feet. The patient was discharged from the hospital on a basic diet and asked to continue adding new foods as she had done in the hospital. With the addition of eggs to her diet, a decided flare up occurred, which necessitated rehospitalization because of the secondary infection which developed. During the second hospitalization, it was found, after a base line had again been reached, that vesicular flares were produced by cream of wheat and corn.

DISCUSSION

DR. JAMES M. FLOOD: This patient well illustrates the etiologic difficulties that one finds in recurrent vesicular dermatitis of the hands and feet. She was found sensitive to her footwear, and even when she stopped wearing shoes to which she was sensitive she continued to have vesiculation on the feet, although she was somewhat improved. At some time she has had a fungous infection with sensitization as evidenced by the trichophytin test. In cases of this kind it is important to differentiate the new vesicles from the old ones when one is determining the food allergies. This woman has been tested for sensitivity to foods by giving her one food a day. In addition to the food allergy and the contact factor, she is very

sensitive to streptococci. She has had two pyogenic flare ups which developed from the food allergy flare ups. The first cleared rapidly with local penicillin therapy, and tonight she seems to have something in addition. I believe that a sensitivity to penicillin has developed.

DR. DONALD M. PILLSBURY: This is in line with Gardner Hopkins' observation that 25 per cent of patients with chronic eczematous eruptions will experience a sensitivity to penicillin.

DR. JAMES M. FLOOD: In our patient, reactions to foods occur in about eight hours; vesicles appear in about twelve hours. Reactions are practically always evident within twenty-four hours.

DR. JOHN H. STOKES: In developing the so-called basal nonallergic diet type of procedure, we started out to determine what the patient is sensitive to, and, incidentally, to find out what he is not sensitive to. We began with the so-called allergic diary and in that way picked out pears in our first case as an allergen. Then we used the Rowe type of diet in an effort to put the patient on a type of diet which rarely causes allergic response. We very soon gave it up. Now we use what we call the B-N-A diet (Basal Nonallergic diet). With this procedure it is possible to find out what foods cause flare ups and to put the patient on a diet which does not cause them. It is to be pursued unaltered for at least six months after the work-up is completed. Many patients are apparently allergic to milk, so that we no longer start with milk after cleaning the intestinal tract with castor oil. The patient, after six or seven weeks, is equipped with a simple diet of meats, cereals, starches, vegetables and fruits which have not excited any lesions, and on that diet he lives for not less than six months. Thus, by maintaining him on a diet to which he has been experimentally proved not to be reactive, he is desensitized to a wide variety of other foods with which he has not even been tested and finally resumes something approximating a normal diet. I think that this procedure ought to be more widely used than it is. The patient can develop the diet for himself.

Lymphocytoma Cutis. Presented by DR. JOHN W. LENTZ and DR. HERMAN BEERMAN.

E. K., a white man aged 27 years, presents a patchy lichenified coalescent brown-yellow papular dermatosis of the abdominal wall. Many papules have seemingly collected about hair follicles. The condition began asymptomatically about ten years ago, with pruritus the only symptom; the condition is more pronounced when perspiration is excessive. The biopsy specimen showed lymphocytoma cutis (foci of lymphocytes in reticulum, occasional giant cell, parafollicular distribution).

DISCUSSION

DR. FRED D. WEIDMAN: This is another illustration of what I said before about the picture's not fitting precisely into any of the recognized dermatologic patterns.

DR. JOHN H. STOKES: I was struck by the possibility of lichen nitidus due to vitamin A deficiency.

DR. DONALD M. PILLSBURY: Lichen nitidus was the first on our list of clinical diagnoses.

Erythema Nodosum with Rheumatic Fever. Presented by DR. A. T. GIORDANO (by invitation) and DR. JOHN F. WILSON.

J. Schildkraut, M.D., *Chairman*

Douglass A. Decker, M.D., *Secretary*

Sept. 20, 1946

Keratoderma Punctatum of Palms and Soles. Presented by DR. MARJORY K. HARDY and DR. CARMEN C. THOMAS.

E. S., a white woman aged 37 years, presents on the palms small, firm, horny, noninflammatory, spicule-like keratotic projections. When one of the lesions is forcibly removed, a small pit remains. The dorsa of the hands are normal. There are similar but fewer lesions on the soles. The dermatosis began when the patient was 16 years of age. One sister, now dead, is said to have been similarly affected. There is no history of ingestion of arsenic. The Wassermann reaction of the blood was negative for syphilis.

The report on the biopsy specimen was: pronounced hyperkeratosis, some acanthosis and no inflammation, but some papillary spaces resembling lymph spaces, which may be artefacts. The patient has received 75,000 units of vitamin A daily for five months and an emollient ointment locally. There has been no change.

(Hydroa Puerorum?) Urticaria Pigmentosa. Presented by DR. JOHN H. STOKES and (by invitation) DR. STEPHEN T. WHELAN.

C. W. C., a white boy aged 2½ years, presents normal skin texture with dermographism limited to areas of brown-red pigmentation which are scattered over the entire body surface. The disease was present at birth. The process appeared first on the face and chest as small bullae with furunculosis and then spread over the entire body, arms, legs and scalp. The bullae disappeared when the patient was 3 months of age, and there have been none since. The patient has wheals which leave pigmented macules. Urticarial lesions always develop in areas of pigmentation, and the patient is dermographic in these spots.

Calcium wafers, tincture of belladonna, 2 minims three times daily, ascorbic acid, 100 mg. twice daily, and diphenhydramine hydrochloride (benadryl®), 25 mg. twice daily, have been administered but the pigmentation remains unaltered. Urticarial lesions are still developing, but not as strikingly as formerly.

DISCUSSION

DR. FRED D. WEIDMAN: Apparently this diagnosis is made because whealing is present. Is there anything to support that diagnosis besides the whealing? The lesions are not yellow, as they should be, and the dermographism can be a nonspecific reaction, occurring in a variety of different dermatoses, so that I do not think that this should be considered a case of urticaria pigmentosa on the evidence at hand. Has the possibility of hydroa puerorum been thought of? There were vesicles and furuncles at first which would fit in with that diagnosis, together with the pigmentation and scarring which occurs in dermatitis herpetiformis.

DR. JOHN H. STOKES: I was not able to elicit any history of vesicles or pustules. The fact that the eruption is limited to the covered parts of the body and the fact that the child has been exposed to the sun without unfavorable

reactions do not fit the diagnosis of hydroa puerorum. One of the reasons I asked the patient to come is that the eruption lacks many of the characteristics of urticaria pigmentosa. The lesions apparently do give rise to scarring. I thought it a case of urticaria with pigmentation. That is just a shift in terminology, and there are no histologic changes to bear this out. I am not prepared to make a definite diagnosis.

DR. STEPHEN T. WHELAN (by invitation): The child had dermographism limited to the areas of pigmentation. The normal skin has never exhibited any dermographism.

Localized Amyloidosis Cutis of the Legs. Presented by DR. LESLIE NICHOLAS.

Keratosis Palmaris et Plantaris (Acquired). Presented by DR. H. E. TWINING.

Paget's Disease of the Breast. Presented by DR. JOHN W. LENTZ, DR. MEYER L. NIEDELMAN and (by invitation) DR. GERLACH MAHONEY.

Chronic Cheilitis of Undertermined Origin; Photosensitivity. Presented by DR. DONALD M. PILLSBURY.

Arsenical Dermatitis Successfully Treated with BAL. Presented by DR. CARMEN C. THOMAS.

Pityriasis Rubra Pilaris. Presented by DR. H. E. TWINING.

Leiomyoma Cutis (Zosteriform). Presented by DR. W. N. NEW, United States Navy, United States Naval Hospital, Philadelphia (by invitation).

F. J. P., a white man aged 25 years, well developed, well nourished and in apparently good health, presents on the back and right loin a wedge-shaped group of discrets papules and nodules, slightly reddened, nodular and intradermal in the region of the cutaneous distribution of the tenth thoracic nerve. The nodules are firm, slightly tender and not fixed to underlying structures and vary in size from 2 mm. to 10 mm. Some give the appearance of following the lines of cleavage in a linear fashion. Lesions are present on the right side of the face and the right side of the neck, reaching up to the hair line. They are discrete and slightly reddened and appear more transparent than the lesions on the back. They vary in size up to 8 mm. Approximately ten years ago the patient noticed papules on the right side of the back and face. He has noticed a burning sensation of the lesions on the back during the past two years, especially when emotionally upset. The results of laboratory tests are essentially negative.

In the lower part of the dermis there were groups and strands of smooth muscle. One of them was a longitudinal section which was adjacent to a hair follicle and might represent hypertrophy of the levator muscle adjacent to this hair follicle. In other areas, smooth muscle fibers were seen in cross section. Histologically, this specimen indicated a leiomyoma. The patient has been seen by plastic surgeons, who advised that the lesions were too widespread for surgical removal.

DISCUSSION

DR. FRED D. WEIDMAN: I think that all of us were struck by the unilateral distribution of the lesions. Those on the face were definitely unilateral, and the ones on the loin began sharply at the line of the spinous processes. The distribution was similar to that of herpes zoster. This makes me wonder whether there is a congenital factor determining a distribution of that sort. That is something that appears to be connected with the somites, and in the sections it seemed that these fibers were related to hair follicles, so that this disease with unilateral distribution and distribution along the somites might be a simple hamartomatous abnormality of the involuntary muscles of the hair follicles, not a true neoplasm.

DR. JOHN H. STOKES: Do any changes occur in the lesion on stroking? Is it painful?

CAPTAIN ROBERT L. GILMAN: Yes. This man's main complaint has been one of pain, particularly on pressure and friction of the clothing. We should like some suggestions as to treatment. A plastic surgeon, did not think that plastic surgery would offer him very much. The patient wants something done, and we were tempted to try fulguration. He is genuinely disturbed by the symptoms particularly over the back.

DR. M. H. SAMITZ: The lesions on the trunk were painful; he winced when I touched them; but those on the cheek were not painful and he shaves every day but complains of no pain while shaving. I suggest the use of solid carbon dioxide.

DR. JAMES T. FLOOD (by invitation): Paravertebral block might be helpful.

A Case for Diagnosis (Lichen Simplex Chronicus; Lichen Planus). Presented by DR. CARMEN C. THOMAS.

J. W., a white man aged 53 years, well developed and healthy, presents a normal skin except for a lesion limited to the left buttock. This is sharply circumscribed and is about the size of a large palm. The upper left border seems most active and has a nodular serpiginous border with considerable induration. The right upper border stops short of the gluteal cleft, which is not involved. The entire right border shows considerable atrophic scarring, which is present also in the lower center of the lesion. The lower outer border is scaly and at places is fissured. There is scaling of the central parts of the lesion. The mucous membranes are not involved. The lymph nodes are normal. The liver and spleen are not enlarged. The cutaneous lesion has been present on the left buttock for seventeen years, beginning as a small scaling patch which gradually extended to the present size. It is somewhat itchy and painful when it becomes fissured.

The Kolmer and Kline reactions of the blood for syphilis were negative. A biopsy specimen taken on Aug. 10, 1946, was reported by Dr. Beerman and Dr. Weidman as representative of hypertrophic lichen planus. The epidermis showed hyperkeratosis and vacuolation in the basal layers. There was a densely packed infiltrate in the upper part of the corium and extending into the basal layers, composed of large clear cells, and also several areas of lymphocytic infiltrate in the corium.

In the past the patient has been treated with an unknown amount of roentgen rays and by means of injections of undetermined nature. Since coming under my care on August 9, local treatment has been with Pragmatar® (ointment for

mycotic and seborrheic conditions of the skin) and ultraviolet rays, with only slight improvement. He has also received roentgen therapy, a total of 100 r through a 1 mm. aluminum filter.

DISCUSSION

DR. MORRIS MARKOWITZ: I think that the disease is lichen simplex of Vidal of the hypertrophic type. It has the crisscross markings.

DR. M. H. SAMITZ: This man said that the dermatosis began as a small patch which he scratched and the present condition developed from that. I think that it is lichen simplex of Vidal.

DR. FRED D. WEIDMAN: I think that we can exclude the diagnosis of lichen simplex of Vidal. There is an extremely dense infiltration of cells, something that one never sees in lichen simplex of Vidal. Maybe it is premycotic mycosis fungoides, but that is difficult to diagnose in any circumstances.

DR. HERMAN BEERMAN: I understand that this is gigantic lichenification. I call attention again to the articles of Ronchese (Neurodermatitis with Giant Lichenification, ARCH. DERMAT. & SYPH. **43**:920, 1941), and Berlin (Lichenificatio Gigantea, ARCH. DERMAT. & SYPH. **30**:1012 [June] 1939) in this connection.

DR. VAUGHN C. GARNER: One thing appears to me to contradict the diagnosis of lichen simplex of Vidal, namely, the sharp circumscription of this lesion with an indurated border. In lichenifications there is a confluence at the center but toward the border the lichenification becomes sparse and more or less discrete. It impressed me clinically as being some type of granuloma. The thick corded sharply circumscribed border is difficult to reconcile with a diagnosis of simple lichenification.

DR. CARMEN C. THOMAS: There has been considerable difference of opinion as to diagnosis on the part of the various pathologists who have studied the sections. Some favored lichen planus, a diagnosis which does not conform to the clinical picture, and others a diagnosis of lymphoblastoma. This would be most unusual in a 17 year old lesion limited to one site. Although in the beginning the lesion may have been pruritic, the patient now complains of little itching and does not scratch frequently. I do not believe that it can be the result of scratching.

DR. REUBEN FRIEDMAN: I suggest application of solid carbon dioxide.

DR. MORRIS MARKOWITZ: Pure coal tar applied every day, painted one coat on top of the other, would produce desquamation with improvement.

Tuberculous (?) Infection of the Buttocks and Perianal Region. Presented by DR. CARMEN C. THOMAS.

R. G., a white man aged 35 years, has both buttocks perforated by numerous sinuses which discharge a gray-yellow, thin pus with a fecal odor. On the left side of the ischium a recent, as yet unperforated, lesion which is tender, but not hot, is forming. Many sinus tracts are open about the perineum, where there is considerable epithelial hypertrophy and the skin is thrown into folds with papillary projections. There is no encroachment palpable on the rectal lumen. There is bilateral inguinal adenopathy. In 1940 a small perianal (ischiorectal?) abscess was drained surgically, and, shortly after, a number of draining sinuses developed around the anus, later involving the buttocks and perineum and requiring a number of surgical drainages, although many perforate spontaneously. There has been a loss of 20 pounds (9 Kg.) in weight in six months.

The patient, who is now pale and thin, said that he was well until the present illness. The medical examination revealed no abnormalties. Proctoscopic examination of 25 cm. of the lower bowel showed nothing abnormal and nothing apparently related to the draining sinuses, although no injection technic was employed.

The blood sugar was 89 mg. and the urea nitrogen 14 mg. The urine was normal. The serum protein was 8.0 and albumen 49. A complete blood cell count resulted in normal observations. Cultures of pus were repeatedly negative for fungi on direct examination and culture. Bacteriologic examination was repeatedly negative for tubercle bacilli. Bacillus proteus was recovered twice, also diphtheroids and a few hemolytic streptococci. The Kolmer and Kline reactions of the blood for syphilis were negative. In the intravenous congo red test, 80 per cent of the dye was recovered in 1 hour. The reaction to the Frei test was negative. The result of the tuberculin test, employing 0.00002 mg. of purified protein derivative, was 2 plus. A roentgenogram of the chest showed healed shadows in the upper lobe of the right lung but no activity. A roentgenogram of the sacrum and lumbar part of the spine made on July 31, 1946, showed superficial bone destruction of the first sacral segment. There were no other abnormalties.

DISCUSSION

DR. REUBEN FRIEDMAN: I do not believe that too much significance need be given to the positive tuberculin reaction nor to the fact that the roentgenogram showed shadows in the upper part of the chest. Considerable significance should be given to the localization of the lesions and their multiplicity, the numerous sinuses, the purulent character of the discharge, the chronicity and unresponsiveness to treatment and the failure to find tubercle bacilli in the discharges. In the circumstances, I suggest a diagnosis of hidradenitis suppurativa.

DR. JOHN H. STOKES: It does not necessarily follow that, because a man has tuberculous lesions elsewhere or a positive tuberculin reaction, this has to be tubercuolus. One sees in certain young persons a most resistant canalizing pyogenic folliculitis of the buttocks which lasts for years, scarring the whole buttock, and the only thing I know of that it responds to is intramuscular injections of a turpentine solution in olive oil. That is on the principle of the old time Netter's abscess treatment for chronic infection—the provocation of a violent reaction in the deep muscle tissue by the use of an agent like turpentine. I have treated 1 or 2 patients in that way, and it works well, though it is a long-drawn-out affair. Then the manganese salts are useful in some of these patients, given intramuscularly, also over a considerable period of time. Potassium permanganate sitz baths produce a striking change. One ought to use the proctoscope, to rule out a tuberculous bowel, fistula in ano and so forth. Roentgen ray therapy was not conspicuously successful, in my experience. Adequate high voltage roentgen ray therapy, however, might help.

DR. M. H. SAMITZ: I would suggest that a culture be made. If penicillin is useless, tyrothricin in one of the new penetrating vehicles might be efficacious.

DR. HERBERT J. SMITH: I think that it is hidradenitis suppurativa.

DR. CARMEN C. THOMAS: The organisms which were found were tested for streptomycin and penicillin resistance and were found to be sensitive to both. I chose penicillin because it is more readily available. A proctoscopic examination gave no information. I might say that the lesions begin deep in the tissues

and are then not at all red. They gradually work to the surface and eventually perforate. I think that there must be a deep focus, which is against the diagnosis of hidradenitis supprativa.

Severe Pyogenic Sycosis of the Beard (Lymphedema? Submental Reigon). Presented by DR. CARMEN C. THOMAS.

Noduloulcerative Syphilide of the Body, Gumma of the Scalp (Radiodermatitis with Ulcer?). Presented by DR. CARMEN C. THOMAS.

Widespread Lupus Erythematosus with Depigmentation in a Negro? (Lichen Planus?). Presented by DR. CARMEN C. THOMAS.

J. M. Schildkraut, M.D., *Chairman*

Douglass A. Decker, M.D., *Secretary*

Nov. 15, 1946

A Case for Diagnosis. (Necrobiosis Lipoidica Without Hyperglycemia?). Presented by DR. EDWARD F. CORSON.

Pityriasis Rubra Pilaris Improved by Treatment with Vitamin A. Presented by DR. KNOLL for DR. FRANK C. KNOWLES.

Familial Benign Chronic Pemphigus (Hailey and Hailey Disease). Presented by DR. ARTHUR G. PRATT.

M. S., a white woman aged 35 years, first had blisters on the sides of her neck five years ago. After several months, the rash healed, leaving residual pigmentation. This has recurred constantly, and the patient has been free of the rash only about two months at any time during the past five years. At the height of an attack, an area approximately 10 by 7 cm. at each side of the neck is covered with an oozing, crusted patch of vesiculation and pustulation. During the interval of healing, the areas show only residual grayish pigmentation. In each axilla there is mild seborrheic dermatitis.

The patient's father and her paternal grandmother have had a chronic rash of unknown type in the axillas for years. Her five brothers and one sister are normal. The medical examination resulted in normal observations. The result of the Mazzini test for syphilis was negative. The blood cell count was normal except for 7 per cent eosinophils.

The report on the biopsy specimen showed slight hyperplasia of the rete cells with decided acantholysis. Numerous leukocytes were found on the surface of the epidermis as well as in the corium. There was moderate downward extension of the rete pegs and considerable edema of the corium, especially in the papillary portion, with vascular dilatation.

The patient was given 1.5 Gm. of sulfapyridine daily for seven days, with complete healing of the lesion except for pigmentation. Boric acid ointment was used locally.

DISCUSSION

DR. FRED D. WEIDMAN: I agree with the diagnosis because I saw the section, but tonight it is not clinically distinctive. The histologic picture is distinctive except that in this particular lesion there is more suppuration than usual; that, of course, could very well be secondary infection. Most of us are aware of the

dispute that has been going on as to whether this is a bullous form of Darier's disease. The Baltimore school, for example, adheres to the Darier thesis, and I think that those who saw the sections will agree that in this case, as in the other cases, there is not any feature of importance with respect to hyperkeratosis. In my judgment, whatever Hailey and Hailey's concept may turn out to be, it will not be Darier's disease.

DR. DONALD M. PILLSBURY: Do you think it a virus infection?

DR. FRED D. WEIDMAN: I think so in the same sense that some think pemphigus a virus disease.

DR. DONALD M. PILLSBURY: Do you believe that on the basis of histologic changes dermatitis herpetiformis can be ruled out?

DR. FRED D. WEIDMAN: In this patient, yes. There are distinctive lacunas in this disease comparable to those which appear in Darier's disease and which do not appear in dermatitis herpetiformis.

DR. DONALD M. PILLSBURY: There is an interesting history. The patient felt that the lesions tended to appear just before her menses. There seemed to be a menstrual element in the eruption, whatever its nature. I think that it would be interesting to follow her and possibly treat her on that basis. I have recently followed a patient with an eruption very much like this, but was never able to satisfy myself as to the exact diagnosis. She showed fairly good improvement following injections of smallpox vaccine.

DR. WILBERT SACHS, New York (by invitation): I agree with Dr. Weidman that the pathologic picture here is characteristic of the disease and that it is not a type of Darier's disease. It seems to me that the type of dyskeratosis found in Darier's disease does permit the formation of bullous lesions. I cannot agree with the name familial benign pemphigus of Hailey and Hailey, as I feel that it is a form of epidermolysis bullosa. After the lesions disappear, a neurodermatitic type of eruption is left but in these areas, microscopically, one finds lacunas just above the basal cell margin, though these are not clinically manifest.

DR. HERMAN BEERMAN: How would Dr. Sachs distinguish this from Darier's disease histologically?

DR. WILBERT SACHS, New York (by invitation): In this disease the cells are not dyskeratotic. They are larger than normal; the nuclei are well formed and well stained, and corps ronds are absent. Also, I have demonstrated in my article mitotic figures in the nuclei, and one never finds mitotic figures in benign, accelerated dyskeratosis.

A Case for Diagnosis (Lichen Planus?). Presented by DR. G. M. KNOLL for DR. FRANK C. KNOWLES.

Pemphigus Vulgaris (Early or Benign?). Presented by DR. SIGMUND S. GREENBAUM.

Purpuric Pigmented Lichenoid Dermatitis of Gougerot and Blum. Presented by DR. D. M. SIDLICK.

Chloracne. Presented by DR. EDWARD F. CORSON.

Herpes Gestationis (Erythema Multiforme?). Presented by DR. JOHN F. WILSON.

Morphea Type Scleroderma (Dermatomyositis?). Presented by DR. FRANK C. KNOWLES and (by invitation) DR. H. A. LUSCOMBE.

J. M. Schildkraut, M.D., *Chairman*

Douglass A. Decker, M.D., *Secretary*

Jan. 17, 1947

A Case for Diagnosis (Barraquer-Ferre Lipodystrophy?). Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. CONRAD STRITZLER.

About seven years ago a group of brownish patches developed above the right knee in a white woman aged 37 years. There was no swelling, pain or fever. This progressed slowly until at present the inner aspect of the right thigh from the internal condyle to the junction of the middle and upper thirds presents an irregular oval area of greenish yellow discoloration which is atrophic and depressed below the level of the surrounding normal skin. It is 22 cm. in its long diameter and 9 cm. in width. The margin fades into the surrounding normal skin. The skin is harsh, roughened and atrophic, and a few telangiectatic vessels are noted. There is diminution in the subcutaneous fat. The skin is freely movable, and there is no associated pain or tenderness. The neurologic examination, an air myelogram and roentgenograms of the spine revealed no abnormalities. The blood count, urinalysis and serologic tests of the blood for syphilis gave negative results.

The histologic section showed atrophy of the epidermis. There were no inflammatory changes in the corium or subcutaneous tissue. Sweat glands and sebaceous glands were preserved.

DISCUSSION

DR. MORRIS MARKOWITZ: The cholesterol and ester contents are normal, and in lipodystrophy one would expect some disturbance in the cholesterol content.

DR. REUBEN FRIEDMAN: There is also an associated muscular disturbance involving the interosseous spaces on the same side, and there is slight atrophy in the left hand. The process is one of muscular atrophy.

DR. SIGMUND S. GREENBAUM: I think this is a case of panniculitis of the nonfebrile type. There is atrophy of the adipose tissue, but I could not see any muscle atrophy as she stretched both legs for comparison.

DR. REUBEN FRIEDMAN: The patient has never had any nodules, pain or fever. Sections failed to reveal signs of panniculitis or inflammation.

Pseudopelade (Folliculitis Decalvans?). Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. CONRAD STRITZLER.

B. M., a white man aged 28 years, well nourished and well developed, presents an irregular band of alopecia stretching across the middle of the scalp just anterior to the vertex. The follicular orifices are prominent in the periphery of the patch, which is pink and atrophic throughout. A few normal hairs appear here and there throughout the patch. Extracted hairs show a glassy sheath about the roots. The patient spent two and a half years in the desert of south Iran while in the service from 1943 to 1945. During this period the scalp became dry and scaly. Several weeks after his return home, in December 1945, "scabs" developed on the scalp. He was treated with shampoos, ointments and lotions. In July 1946 the "scabs" fell off, and none appeared thereafter.

Tyrothricin has been applied locally. The lesion has not progressed since institution of this therapy.

DR. REUBEN FRIEDMAN: Sutton's book on dermatology considers pseudopelade and folliculitis decalvans as synonymous, while McCarthy goes to considerable trouble to point out that Brocq, who described pseudopelade, differentiated it from

folliculitis decalvans, described by Quinquaud. He insists that pseudopelade is never associated with folliculitis and that it occurs in the form of discrete patches which perhaps may coalesce, as they did in this case, whereas folliculitis decalvans is characterized by uniform folliculitis. Later, in the cicatricial alopecia, they may not be differentiated one from the other, but in the earlier stages they are definitely different.

DR. SIGMUND S. GREENBAUM: Pelade is the French term for alopecia areata. The term pseudopelade would therefore indicate the absence of clinically apparent folliculitis. Pseudopelade is, apparently, a noninflammatory, slowly progressive cicatricial alopecia.

DR. LOUIS GOLDSTEIN: Since he was exposed to the sun, it is possible that the patient had lupus erythematosus, which has subsided, especially since he had crusting on the scalp.

DR. SIGMUND S. GREENBAUM: In lupus erythematosus the lesions usually are circinate in outline; Brocq established the point that in pseudopelade the lesions show a peculiar irregularity, a shooting out of the lesions into the surrounding skin. The glassy sheath, furthermore, is pathognomonic of pseudopelade, so I think the diagnosis is inescapable. Pustulation is essential to folliculitis decalvans, and there certainly is no pustulation here, and the patient gives no history of a previous pyogenic eruption.

Acne Necrotica Miliaris. Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. CONRAD STRITZLER.

R. E., a white man aged 42 years, when first examined in October 1945, showed the scalp studded with hundreds of pinhead to match head-sized, reddish brown papules with crusted, necrotic, depressed summits. Many appeared in the hairline and many in the bearded region, and there were about thirty lesions in the interscapular region. Some had undergone involution, leaving depressed, crateriform, pinhead to match head-sized scars. A few centrally depressed papules were present on the nasal half of each orbital ridge, and one was noted on the left nasolabial fold. The dermatitis began in 1943 with small, itchy lesions of the scalp which slowly increased in number by the addition of small crops. In 1945 similar lesions appeared on the face and back.

Treatment included subfractional doses of roentgen ray; staphylococcus toxoid once weekly for ten weeks; tyrothricin ointment, and penicillin ointment, 500 units a gram in water-miscible base. There was no improvement. The patient improved considerably when given 100,000 units of penicillin in cholesterolized peanut oil daily for six days.

Staphylococcus aureus, nonhemolytic and coagulase positive, was found on culture. Dr. Fred D. Weidman's pathologic diagnosis was resolving folliculitis or acne varioliformis.

DISCUSSION

DR. CARROLL S. WRIGHT: I wish to mention a simple treatment that Dr. Schamberg used to employe—a 1:600 dilution of bichloride of mercury in 70 per cent alcohol. I have seen these cases respond miraculously to this treatment. It might be worth trying in this case, although I admit that the condition is more severe and widespread than any other of this type that I have ever seen.

DR. HERMAN BEERMAN: Could this be a follicular seborrheic dermatitis?

DR. SIGMUND S. GREENBAUM: I wish to take exception to the term "miliaris" as applied to this case since that term is generally applied to the presence of but

a few minute lesions scattered throughout the scalp associated with itching. Often one will see it in women or men who complain only of itching, and then on examination one finds a minute lesion around the hair as it emerges from the follicle. This man has major acne necrotica, and, as Dr. Wright states, it is a simple matter to clear up with either bichloride of mercury or with sulphur, but, as in tinea versicolor and seborrheic dermatitis, treatment must be continued for a long time to prevent recurrences.

DR. REUBEN FRIEDMAN: Dr. Stritzler adds that we did use a 1:1,000 dilution of bichloride of mercury in 70 per cent alcohol but discontinued its use because it was ineffective.

DR. VAUGHN C. GARNER: Montgomery, of the Mayo Clinic, has written extensively on this subject. These lesions certainly are not miliary, and while it definitely conforms to the diagnosis of acne necrotica, I think it differs from the acne miliaris in the Mongomery sense. Montgomery advocates the use of ammoniated mercury in the cases in which the scalp is affected, and several patients whom I have seen have done extremely well under that regimen.

DR. SIGMUND S. GREENBAUM: The best experimental work on acne necrotica was carried on by Dr. Weidman and Dr. Strumia some years ago, in which they demonstrated an organismal cause for acne necrotica. (Experimental Acne Varioliformis, Arch. Derm. & Syph. **10**:702-713, 1924).

Kaposi's Idiopathic Pigmented Sarcoma? Chromoblastomycosis? Presented by DR. REUBEN FRIEDMAN and (by invitation) DR. CONRAD STRITZLER.

A Case for Diagnosis (Erythroplasia?). Presented by DR. SIGMUND S. GREENBAUM.

A. T., a white man aged 31 years, has three fourths of the palate involved with a deep red, well defined patch which has a smooth periphery and a central portion showing irregular elevations which are soft to the touch (almost velvety). Just in front of the soft palate, at the center, there is a slightly infiltrated area. At first it was recurrent, but since 1943 it has been a persistent lesion. The patient first noticed a tender papule in the center of the palate. This was treated with local applications, but the lesion gradually became larger. In July 1944 new dentures were prescribed, and profuse bleeding occurred for twenty-one days after they were worn for two days. Dentures of the "roofless" type were prescribed in June 1945, and within forty-eight hours inflammation, swelling, tenderness and bleeding increased. New dentures of a metallic material (tantalum?) were prescribed in October 1945, which caused an exaggeration of symptoms. At present the patient uses dentures only when eating and during business appointments, approximately two hours a day. The lesion is apparently at a standstill. The patient had streptococcic septicemia on three occasions eight to twelve years ago, while working as a butcher. His mother died at the age of 55 of carcinoma and his father at the age of 59 from an unknown cause. Two brothers and four sisters are all living and well.

Routine laboratory tests resulted in findings that were within normal limits; the Kahn reaction of the blood was negative. A biopsy specimen examined in August at the Naval Hospital in Fort Eustis, Virginia, was reported as chronic inflammatory tissue.

The follow-up report of the second biopsy stated that the specimen included the mucosa and a bit of submucosa. The epithelium of the mucosa was moderately thickened and extended downward in long rete pegs. The cells were not atypical. In the corium there was a dense chronic inflammatory exudate of lymphocytes and

plasma cells mostly, which obscured the basement membrane. There was no evidence of malignancy. The diagnosis was some form of focal chronic inflammation of the palate.

Cicatrizing Epithelioma of the Scalp. Presented by DR. SIGMUND S. GREENBAUM.

Scleroderma. Presented by DR. E. R. GROSS and DR. CARROLL S. WRIGHT.

M. A., a white woman aged 67 years, presents a silver dollar-sized, hard, circumscribed lesion on the left side of the chest. The dorsum of both hands and forearms is thickened and boardlike. There is similar involvement of the extensor surfaces of both legs, with superficial ulceration of the left leg. The disease began with stiffness of all joints, and the backs of the hands became "hardened." These changes spread gradually to the forearms and legs.

The patient has received bismuth sodium triglycollamate (bistrimate®), 225 mg. daily, since July 23, 1946, with great improvement. She says that the sensation of tightness is gone and the skin feels softer and warmer.

J. M. Schildkraut, M.D., *Chairman*

Douglass A. Decker, M.D., *Secretary*

Feb. 21, 1947

Dermatitis Herpetiformis in a Woman Aged 72 Years. Presented by DR. M. H. SAMITZ and (by invitation) DR. P. N. HORVATH.

Lupus Erythematosus with Superimposed Epithelioma? Presented by DR. C. S. LIVINGOOD and (by invitation) DR. K. KATZENSTEIN.

Lipophagic Granuloma at Sites of Intramuscular Injections. Presented by DR. C. S. LIVINGOOD and (by invitation) DR. W. B. SHELLEY.

Chromoblastomycosis (Recurrence in Case Reported in The Archives 43:62 [Jan.] 1941). Presented by DR. DONALD M. PILLSBURY AND DR. IRA L. SCHAMBERG.

Ichthyosis Hystrix. Presented by DR. DONALD M. PILLSBURY, DR. C. S. LIVINGOOD and (by invitation) DR. J. P. SCULLY.

J. P., a white boy aged 2 years, alert and well nourished, presents keratinous, spinous-like processes involving the knees, elbows, forearms, wrists and the lateral surfaces of the neck. Studies of sweating indicate that only the skin of the forehead has normally functioning sweat glands and that temperature control is relatively poor. The maternal grandmother had ten children, five male and five female. Four male children died at or soon after birth, of unknown cause. A maternal aunt has had three pregnancies, with death at birth of the infants, all of whom were male. This patient is the result of his mother's only pregnancy. There was normal, full term, spontaneous delivery. The birth weight of the patient was 7 pounds 9 ounces (3,430 Gm.). When the mother first observed her infant on the third postpartum day, she noted what she described as "large, clear, fluid-filled blisters" on the infant's face and body, with the exception of the palms and soles. These vesicles recurred during the first year and a half of life, but with less and less frequency. When the baby was 6 months old, the mother noted

a tendency of the skin on the elbows, knees, legs and arms to become dry and scaling, then the development of thick keratinous spines as now seen.

The child has been previously given thyroid, "1 tablet three times daily," over a six months' period, without benefit. Breast feeding was discontinued at 3 months, and various other dietary changes were of no benefit. Locally applied ointments were ineffectual.

The dentition, hair and nails are normal. The general health and mental development are excellent. There are no abnormalities except in the skin.

The complete blood cell count was within normal limits. The fasting blood sugar, blood phosphorus and serum cholesterol were within normal limits. The results of serologic tests of the blood for syphilis were negative. The roentgenogram of the chest was normal. The eyes were normal. The diagnosis from biopsy was ichthyosis, hyperkeratosis, acanthosis and vacuolization of the epidermis.

DISCUSSION

DR. JOHN P. SCULLY (by invitation): Does anyone think that high doses of vitamin A might be of some benefit in this case? Could we seriously consider the possibility of these male infant deaths in the family as being due to a dermatologic condition such as this or at least a lipogene in the family tree of which this may be a variant, which would induce us to advise the female members of the family to avoid conception?

DR. MORRIS MARKOWITZ: Ichthyosis hystrix has been treated with sodium chloride baths or ointments with improvement in the condition.

DR. M. H. SAMITZ: To grease a dry skin, one should use either animal or vegetable fat. Greases from the petroleum family will only degrease the skin. I advise the use of wool fat rather than aquaphor® (an oxycholesterol-petrolatum ointment base).

DR. H. H. PERLMAN: I have tried vitamin A in ichthyosis without improvement. I have ceased making vitamin A determinations because the vitamin A content of the vascular system is not necessarily an index of the vitamin A content of the liver.

LIEUTENANT FITZPATRICK (by invitation): When this disease is present at birth, it will probably not respond to the administration of vitamin A. Keratotic diseases that develop during life will respond to the administration of vitamin A.

CAPTAIN R. L. GILMAN: In view of the family history, it would be interesting to get the Rh factors in this boy's parents. I agree with the presenters that this is something more than ichthyosis.

DR. C. S. LIVINGOOD: We had a patient whom we followed closely with controlled areas treated with sodium chloride ointments versus other types of greases, without any significant difference.

DR. MORRIS MARKOWITZ: I have tried sodium chloride therapy in keratosis palmaris et plantaris with considerable success. I have not tried it in ichthyosis.

Keratoderma Palmaris et Plantaris (Improvement with Vitamin A Therapy. Presented by DR. H. H. PERLMAN.

Onychomycosis. Presented by DR. D. M. PILLSBURY, DR. C. S. LIVINGOOD and (by invitation) DR. J. P. SCULLY.

Book Reviews

Common Skin Diseases. By A. C. Roxburgh, M.D. Eighth edition. Price, $7. Pp. 497, with 220 illustrations. Philadelphia: The Blakiston Company, 1948.

This book was written for a general practitioners' series. It is well and generously illustrated. The photographs are excellent, and the subject matter is presented clearly and simply. This last-mentioned attribute necessitates some sacrifice of well rounded opinion, one result being the inclusion of lichen sclerosus et atrophicus as an atrophic form of lichen planus without any comment. Also, the distinctive burning character of the itching in dermatitis herpetiformis is not mentioned.

Because the book was revised in 1947 or earlier, there is no mention of fatty acids in accounts of the treatment of superficial fungous infections. The only mention of antihistaminic drugs is a single line footnote on diphenhydramine hydrochloride (benadryl®). Streptomycin is not mentioned with reference to the treatment of granuloma inguinale or tuberculosis cutis. The treatment of syphilis is not discussed, but the reader is referred to texts on venereal diseases for "the mapharsen and bismuth therapy" without mention of penicillin.

The treatment presented is carefully discussed. However, considering that the book was designed for general practitioners, Whitfield's ointment is overemphasized for the treatment of superficial fungous infections at the expense of blander and less risky measures. Penicillin ointment is recommended for eczema and infectious eczematoid dermatitis, two conditions in treatment of which it may sensitize most easily.

This book is very useful for the instruction of general practitioners. As noted previously, treatment mentioned is not as up-to-date as the book's year of publication in this country might indicate, and the work was not received for review until March 1949.

CORRECTION

In the article by Drs. Curtis and Cawley, in the August issue of the ARCHIVES, the first sentence of the last paragraph on page 140 should read: "In addition to the training already received Dr. Wile accepted on his return to New York a position with Sigmund Pollitzer as instructor in dermatology and syphilology at the Post-Graduate Medical School and Hospital and as his assistant at the Lenox Hill Hospital."